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How excessive anxiety may induce vagal stimulation of acid-pepsin secretion

A manifestation of emotional stress, excessive anxiety may induce gastric hypersecretion by its effect on central and peripheral neural activity. Hypothalamic mediation of *vagal* activity increases acid and pepsin output,[1,2] leading to exacerbation of the distressing symptoms of duodenal ulcer.

Artist's impression of peripheral nerve ramifying on the surface of gastric mucosal cells. Illustration based on a cross section of gastric wall as seen by scanning electron microscope.

1. Sun DCH: Etiology and pathology of peptic ulcer, chap. 27, vol. 1, in *Gastroenterology*, ed. 3, edited by Bockus HL, *et al*. Philadelphia, W.B. Saunders Company, 1974, pp. 586, 592-593. 2. Palmer ED: *Clinical Gastroenterology*, ed. 2. New York, Hoeber Medical Division, Harper & Row, Publishers, 1963, p. 202.

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How excessive anxiety may induce vagal stimulation of acid-pepsin secretion

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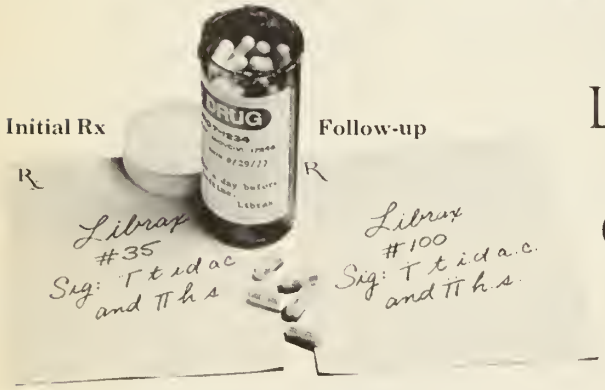

The initial prescription allows evaluation of patient response to therapy.

Follow-up therapy with a prescription for a 2- to 3-week supply of medication usually helps maintain patient gains.

Please consult complete prescribing information, a summary of which follows:

* **Indications:** Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

How Supplied: Available in green capsules, each containing 5 mg chlordiazepoxide HCl (Librium®) and 2.5 mg clidinium Br (Quarzan®)—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 50, singly and in trays of 10.

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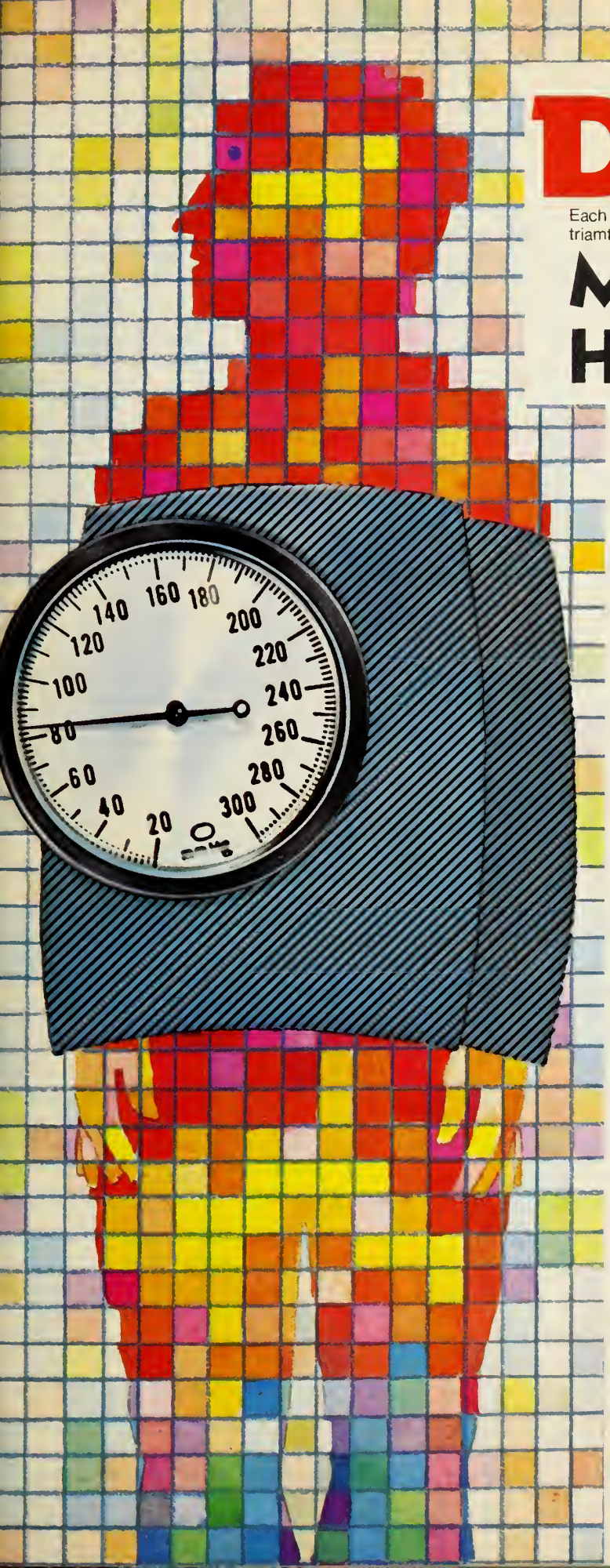

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This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently; both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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Tablets
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Brief Summary of Prescribing Information

DESCRIPTION Each tablet of PERCOCET®-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS. 6085 BS

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Each tablet contains 5 mg oxycodone HCl (WARNING: May be habit forming) and 325 mg acetaminophen (APAP) C II

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- □ indicated for moderate to moderately severe pain
- □ contains well-tolerated acetaminophen
- □ provides the effective analgesia of oxycodone
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CONTRAINDICATION: Topical steroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparations.

PRECAUTIONS:
General—If irritation develops, discontinue the product and institute appropriate therapy. In presence of an infection, institute use of a suitable antibacterial or antifungal agent. If a favorable response does not occur promptly, discontinue the corticosteroid until the infection has been adequately controlled. If extensive areas are treated or if the occlusive technique is used, there will be increased systemic absorption of the corticosteroid and suitable precautions should be taken, particularly in children and infants. These preparations are not for ophthalmic use.
Usage in Pregnancy—Although topical steroids have not been reported to have an adverse effect on human pregnancy, the safety of their use in pregnant women has not been absolutely established. In laboratory animals, increases in incidence of fetal abnormalities have been associated with exposure of gestating females to topical corticosteroids—in some cases at rather low dosage levels. Therefore, drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.
Occlusive Dressing Technique—The use of occlusive dressing increases the percutaneous absorption of corticosteroids. For patients with extensive lesions it may be preferable to use a sequential approach, occluding one portion of the body at a time. Keep the patient under close observation if treated with the occlusive technique over large areas and over a considerable period of time. Occasionally, a patient who has been on prolonged therapy, especially occlusive therapy, may develop symptoms of steroid withdrawal when the medication is stopped. Thermal homeostasis may be impaired if large areas of the body are covered. Discontinue use of the occlusive dressing if elevation of the body temperature occurs.

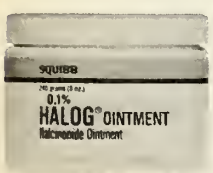
Occasionally, a patient may develop a sensitivity reaction to a particular occlusive dressing material or adhesive and a substitute material may be necessary. If infection develops, discontinue the use of the occlusive dressing and institute appropriate antimicrobial therapy.

ADVERSE REACTIONS: The following local adverse reactions have been reported with topical corticosteroids, especially under occlusive dressings: burning sensations, itching, irritation, dryness, folliculitis, hypertrichosis, acneform eruptions, perioral dermatitis, allergic contact dermatitis, hypopigmentation, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

For full prescribing information, consult package inserts.

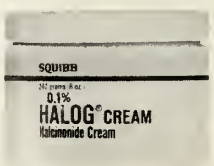
HOW SUPPLIED: The 0.025% and 0.1% Cream and the 0.1% Ointment are supplied in tubes of 15 g and 60 g, and in jars of 240 g (8 oz). The 0.1% Solution is supplied in plastic squeeze bottles of 20 ml and 60 ml.

Halog Ointment 0.1%
Halcinonide Ointment 0.1%



240 g

Halog Cream 0.1%
Halcinonide Cream 0.1%



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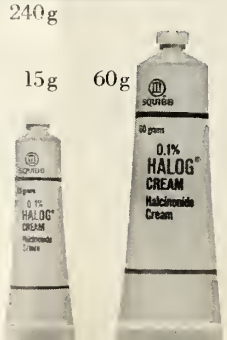
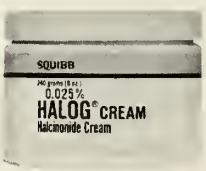


Halog Cream 0.025%
Halcinonide Cream 0.025%



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The 6,000,000 patients already treated with Motrin is an objective measure of physicians' confidence in the ability of Motrin to relieve the pain and inflammation associated with rheumatoid arthritis and osteoarthritis.

So it is not surprising that in this short period Motrin has become the most frequently prescribed alternative to aspirin. Motrin relieves joint pain and inflammation as effectively as indomethacin or aspirin, but causes significantly fewer CNS and milder GI reactions. However, gastrointestinal bleeding, sometimes severe, has been associated with Motrin, aspirin, indomethacin, and other nonsteroidal antiarthritic agents.

*The safety and effectiveness of Motrin have not been established in patients with Functional Class IV rheumatoid arthritis (incapacitated, largely or wholly bedridden, or confined to wheelchair; little or no self-care).

© The Upjohn Company

Motrin 400 mg TABLETS
ibuprofen, Upjohn

The confidence that comes from experience—
one more reason to prescribe Motrin.

Please turn page for a brief summary of prescribing information.

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001

The confidence that comes from experience—
one more reason to prescribe

Motrin 400 mg TABLETS
ibuprofen, Upjohn

Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin* used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin (ibuprofen) is gastrointestinal (4% to 16%). This includes nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness*, headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

Incidence: Unmarked 1% to 3%; *3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

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Unit-dose package of 100	NDC 0009-0750-06
Unit of Use bottles of 120	NDC 0009-0750-26

Caution: Federal law prohibits dispensing without prescription.

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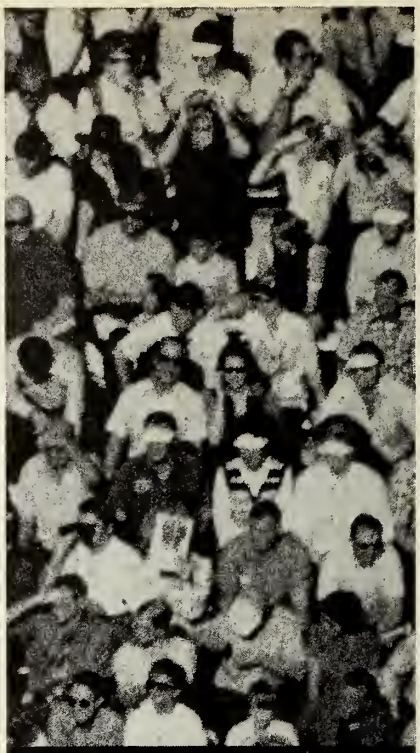

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Refer to: Novey HS, Wells ID: Allergic bronchopulmonary aspergillosis. West J Med 130:1-5, Jan 1979

Allergic Bronchopulmonary Aspergillosis

HAROLD S. NOVEY, MD, *and* IAN D. WELLS, BSc (Tech), *Orange, California*

Allergic bronchopulmonary aspergillosis, a syndrome associated with asthma, manifests with transient pulmonary infiltrates and eosinophilia and can progress to severe proximal bronchiectasis, bronchocentric granulomatosis and pulmonary fibrosis. Early recognition and treatment should favorably influence these complications. Use of the precipitins test with Aspergillus antigens as a screening procedure has identified 99 possible cases in California over a 50-month period. At least 44 cases have been confirmed; and demographic analysis shows that a preponderance of them involved patients less than 35 years old, occurred in farming and rural communities and were discovered in the months of September through February.

ALTHOUGH ALLERGIC bronchopulmonary aspergillosis was first described in 1952[1] and hundreds of cases were reported in England within the next few years,[2] the first cases in the United States were not published until 1968.[3] Since then, most of the case studies have come from medical centers in the Great Lakes and Mississippi River areas.[4-6] We have been interested in determining the prevalence of this disease in California since 1973.

One reason for the paucity of case discovery in the United States has been the absence of a specific diagnostic criterion. The constellation of symptoms and signs produces a highly suggestive picture, but these are individually not unique. The most frequently used laboratory test, the precipitin test for Aspergillus species antigens, is of appropriate sensitivity but is not specific for disease.

Rosenberg and co-workers developed a list of seven major and three minor diagnostic criteria (Table 1). The presence of six of the seven primary criteria was considered very likely diagnostic; if all seven were present, diagnosis was considered certain.[7]

We offered to perform the precipitin test for Aspergillus species on serum specimens submitted to us by physicians from patients whom they suspected of having allergic bronchopulmonary aspergillosis. In many instances, the physicians also submitted a case history or completed a questionnaire form that we provided (Figure 1). This report deals with the cumulative data over a period of approximately four years.

Materials and Methods

Serum specimens were obtained from four sources: (1) patients who were suspected by their physicians of having allergic bronchopulmonary aspergillosis; (2) patients who were suspected by their physicians of having unspecified hypersensitivity lung disease (many of the specimens for categories 1 and 2 were received by mail); (3) consecutive patients who visited the adult allergy and chest clinics at University of California, Irvine, Medical Center, and (4) unaffected persons, including 15 carefully screened

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Submitted, revised, September 11, 1978.

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ABBREVIATIONS USED IN TEXT
RAST = radioallergosorbent test
RIST = radioimmunosorbent test

children (aged 6 to 16) and 19 adults (aged 20 to 40) and 83 other presumably healthy individuals who obtained preemployment blood counts but were not personally interviewed.

There were 1,356 specimens, which were collected between October 1973 and December 1977.

Specimens were stored at 4°C, and immunological tests were done within seven days. All double diffusion and radioallergosorbent tests (RAST) against Aspergillus extracts were done at our laboratory. Other laboratories did some of the total serum IgE tests, but all used the radioimmunosorbent test (RIST, Pharmacia Fine Chemicals, Piscataway, New Jersey).

Most antigens used for skin tests were an Aspergillus mixture (Hollister-Stier Corp., Spokane, Washington), and most tests were performed by the physicians who submitted the samples. For scratch or prick skin tests 1:20 weight/volume was used and for intracutaneous tests 0.01 to 0.1 ml of 1:1,000 concentration was used. The criteria for reporting results varied.

Antigens for double diffusion in gel and RAST were prepared from the following sources: Aspergillus fumigatus, strain A, obtained from J. Pepys' laboratory, Brompton Hospital, London, and kept frozen at −40°C; strain B, culture of patient, S.J., University of California, Irvine, Medical

TABLE 1.—*Criteria for the Diagnosis of Allergic Bronchopulmonary Aspergillosis*[7]

Primary
Episodic bronchial obstruction (asthma)
Peripheral blood eosinophilia
Immediate skin reactivity to Aspergillus antigen
Precipitating antibodies against Aspergillus antigen
Elevated serum immunoglobulin E concentrations
History of pulmonary infiltrates (transient or fixed)
Central bronchiectasis
Secondary
Aspergillus fumigatus in sputum (by repeated culture or microscopic examination)
History of expectoration of brown plugs or flecks
Arthus reactivity (late skin reactivity) to Aspergillus antigen

TABLE 2.—*Incidence of Precipitins to Aspergillus Species (October 1973 to December 1977)*

Source of Specimens	*Number Tested*	*Number Positive*	*Percent Positive*
Patients suspected for allergic bronchopulmonary aspergillosis	442	205	46
Patients suspected for hypersensitivity pneumonitides	536	97	18
Patients of Allergy and Chest Clinic	261	45	17
Unaffected persons	117	2	2
TOTALS	1,356	349	27

HYPERSENSITIVITY PNEUMONITIDES: ASPERGILLOSIS QUESTIONNAIRE

CLINICAL DATA

Patient's name, birth date, pertinent symptoms, diagnostic impressions; results and dates of x-ray films of chest, complete blood counts, cultures, skin tests, studies of pulmonary functions, brief summary of pertinent findings.

SOURCES OF EXPOSURE

Occupation (duration); hobbies (duration); pets (name, number, intimacy, duration); contacts (home, work, visits, neighborhood); nature and duration of contact with: poultry, birds, farms, cattle, compost or manure, hay, stables, barns, other comparable or suspected exposures; air conditioning (home or work and type, humidifiers or vaporizers used).

Physician's Name, Hospital or Laboratory, and Date.

Figure 1.—Summary of information covered by questionnaire form used by physicians who submitted serum specimens from patients suspected of having allergic bronchopulmonary aspergillosis.

TABLE 3.—*Demographic Data for Patients With Probable and Possible Allergic Bronchopulmonary Aspergillosis*

	Probable ABPA	*Possible ABPA*
Number of patients	44	45
Median age, years	32	44
Age range, years	10-71 (7 over 50)	6-68 (10 over 50)
Sex, male/female	22/22	17/25 (3 undesignated)
Geographical areas*		
Rural (mostly Sacramento and San Joaquin valleys)	43%	41%
Urban (greater Los Angeles)	47%	49%
Serum specimen obtained in six-month period from September through February†	71%	71%

*Of all serum specimens, 34 percent were from patients in rural areas.

†Of all serum specimens, 52 percent were obtained in this period.

TABLE 4.—*Diagnostic Features of Allergic Bronchopulmonary Aspergillosis in 44 Patients in California*

Suggested Criteria[a]	*Number of Patients Tested*	*Percent Positive*
Primary		
Asthma	44	100
Peripheral blood eosinophilia when off steroids	44	100
Immediate skin reactivity to Aspergillus antigen	32	91
Serum immunoglobulin E antibody to Aspergillus antigen*	14	100
Precipitins to Aspergillus antigen	44	100
Elevated serum immunoglobulin E	10	100
History of pulmonary infiltrates	44	96
Central bronchiectasis	9	100
Secondary		
Aspergillus fumigatus in sputum	22	59
History of expectoration of brown plugs or flecks	44	7
Arthus reactivity to Aspergillus antigen	21	81

*By radioallergosorbent test (RAST).

Center, obtained from lobectomy specimen; A. terreus, niger, fisherii, ochraceus, and nidulans, obtained either from reference laboratories or from patient sources. The potency and reliability of the antigens were tested in proved cases of allergic bronchopulmonary aspergillosis. The method of preparation and demonstration of precipitins and specific IgE antibodies to Aspergillus have been previously described.[8] For the RAST, antigen was attached to cyanogen bromide activated microcellulose beads.

Results

Screening Precipitin Data

The results are summarized in Table 2. The prevalence of precipitins was highest in specimens from patients whose physicians suspected allergic bronchopulmonary aspergillosis. Of the patients in other categories with positive precipitins, several were examined, and no evidence of clinical disease ascribable to Aspergillus organisms was found. Therefore, the finding of precipitins is not pathognomonic of disease but probably does indicate exposure to the antigen. Based on the presence of Aspergillus precipitins, there were 349 potential candidates for the disease, of whom 205 were thought by their physicians to have allergic bronchopulmonary aspergillosis.

Clinical Data

Of the 442 patients suspected for allergic bronchopulmonary aspergillosis, there were few or no data on about half of them. For the rest, sufficient information was available to make a highly probable diagnosis of allergic bronchopulmonary aspergillosis in 44, aspergilloma in 3 and either aspergilloma or invasive aspergillosis (or both) in 3. For 45 others there were two or more criteria for the diagnosis but data were incomplete; these were grouped in the category of possible allergic bronchopulmonary aspergillosis. All had positive precipitins to Aspergillus except for two patients in the possible category.

Demographic data are given in Table 3. Analyses of these data showed a preponderance of patients less than 35 years old (75 percent), concentrated in rural and farming communities, whose disease was discovered during the six fall and winter months from September through February. Of 44 confirmed cases, we had environmental data for 27; of these 18 had conceivable exposure to sources of Aspergillus contamination as follows: eight were farmers with livestock, barns, hay and compost; four raised chickens or other birds; three had moldy bathroom walls covering leaky water pipes; two were cabinet and wood workers, and one was a garbage collector. On the three occasions in which culture plates for fungi were exposed in homes, large growths of Aspergillus species were found.

Immunological Data

Table 4 presents salient clinical features for the confirmed cases. All patients had multiple precipitins to Aspergillus antigens except one who

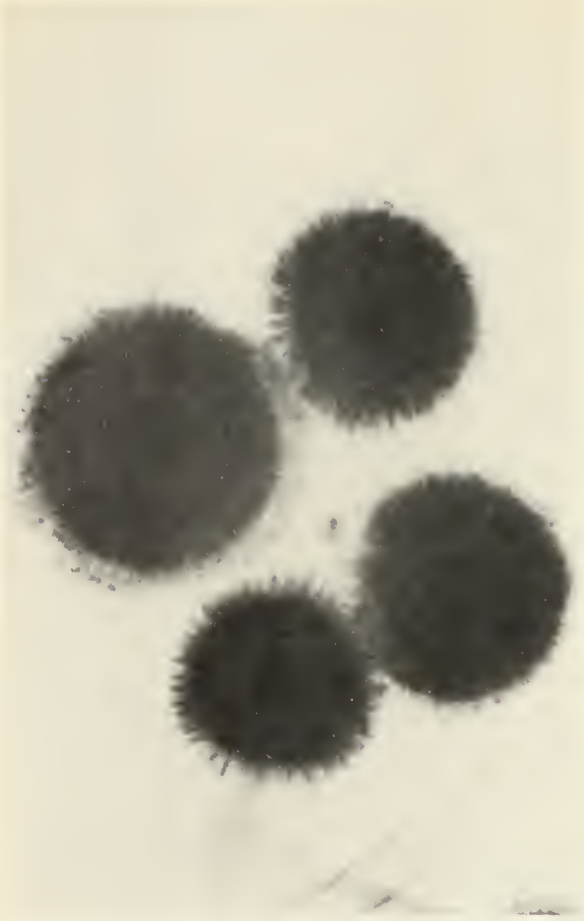

Figure 2.—Aspergillus ochraceus in a patient with allergic bronchopulmonary aspergillosis, ×400, india ink mount from a sputum culture. Note the sunburst effect produced by the large conidial head, its radiating sterigmata, and the attached spores about 2.5 microns in diameter.

had a single arc. Specimens from all patients with confirmed diagnosis reacted to A. fumigatus, with two exceptions. These exceptions reacted to A. ochraceus, a species not previously incriminated in allergic bronchopulmonary aspergillosis;[9] however, subsequent specimens from the same patients did also react to A. fumigatus (Figure 2). Among the A. fumigatus reactions, there were some with more bands to other species, especially A. terreus. We could read up to 13 lines on the Ouchterlony plates in a patient with an aspergilloma. The average total for the seven antigens was 5.8 lines (Figure 3). The serum IgE levels ranged from 1,000 to 15,220 IU, well above the upper normal limit of 300.

Ten patients were studied for periods ranging from three months to four years, with three to 20 immunoserological tests each. These studies indicated a tendency toward direct correlation between severity of symptoms and number of precipitins. In patients with complete remission of symptoms, the precipitins tended either to disappear or decrease appreciably and to recur during clinical exacerbations. A patient previously reported[8] had serial precipitin tests after a lobectomy for allergic bronchopulmonary aspergillosis and bronchocentric granulomatosis (Figure 4). In that case, precipitins decreased 60 percent during the first postoperative month, another 40 percent during the next month, and were undetected at the end of the third month. There was no such correlation with IgE antibodies, which tended to remain present even in remissions. The

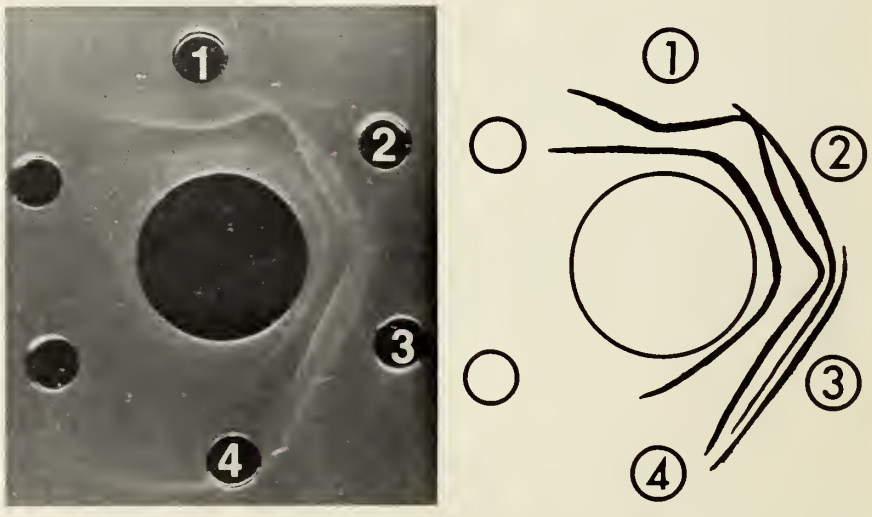

Figure 3.—Photograph and clarifying sketch of precipitin lines from a patient's serum (large central well) and antigens to (1) Aspergillus terreus, (2) A. fumigatus (Brompton source), (3) A. fumigatus (patient, S.J., University of California, Irvine), and (4 and two unnumbered wells) antigens from other Aspergillus species. Only antigens from wells 1, 2, and 3 react with the patient's serum to form precipitins. Outermost line reacts only with well 3 above, the next is a reaction of identity between wells 2 and 3, while the inner two show identity with antigens from wells 1, 2, and 3. There are a total of nine lines with the six Aspergillus extracts and the patient's serum. On the photograph, the line seen emerging from well 4 is a reaction from an adjoining test and is unrelated to this study.

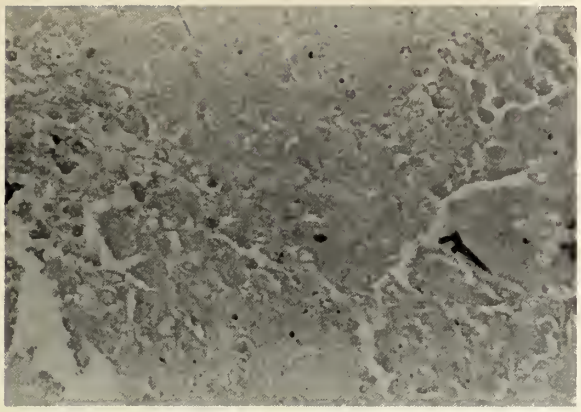

Figure 4.—Branching septate fungal hyphae compatible with Aspergillus species present in mucous material in dilated bronchus, lobectomy specimen from a 14-year-old boy with allergic bronchopulmonary aspergillosis. (Gomori methenamine-silver nitrate stain with hematoxylin counterstain ×1757). There was no fungal invasion of the tissue.

data are insufficient to indicate any trend with total serum IgE.

Discussion

Although the syndrome of allergic bronchopulmonary aspergillosis was first described about 25 years ago, it probably did not originate then, since the association between asthma and transient pulmonary infiltrates with eosinophilia and asthma and bronchiectasis had been recognized for decades before. What is now better understood is that Aspergillus, a fungus, can produce a pulmonary disease similar to tropical eosinophilia associated wth microfilariae and that Aspergillus antigens evoke both specific and nonspecific responses by the IgE system.[10] Also recognized is a definite link between recurring infiltrates and bronchiectasis, both of which tend to occur in proximity of the larger bronchi. Bronchial challenges, pathological and immunological studies in primates and humans indicate that the disease is caused not by fungal invasion but by hypersensitivity reactions to fungal antigens. The spores of Aspergillus average about 2.5 microns in diameter, which is a convenient size for bronchial deposition, and their inherent antigenicity is at least partly responsible for their pathogenetic role.

The immunodiffusion test for Aspergillus precipitins and perhaps the immediate skin test reaction serve well as screening tests for case detection. The discovery by one consultation service of at least 11 new cases yearly in California suggests that allergic bronchopulmonary aspergillosis is not rare. There may well be an interrelation between the preponderance of cases in the younger ages, in farm areas, and in the fall and winter months. The greater physical activity and immune response in youth may enhance contact and reaction with heavier than normal concentrations of Aspergillus.

Higher spore counts and disease rate have been documented in rural Wales during the rainy season.[11] Aspergillus is the major fungal pathogen of birds and fowl;[12] moldy hay and compost serve as culture media. Aspergillus is a ubiquitous organism. Even in an urban area of northern California, it was the third most common fungus identified in one survey.[13]

Efforts to diagnose allergic bronchopulmonary aspergillosis are mandatory to prevent progress of reversible airways disease to permanent damage. Early treatment with systemic steroids and removal from sources of heavy exposure are believed successful in preventing bronchiectasis and pulmonary fibrosis.

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Follow-up Study of Patients With Cerebral Palsy

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Of 319 patients with cerebral palsy recalled for reevaluation 15 years after the initial visit, 10 percent had died. Of the living, 55 percent had spasticity, 32 percent had athetosis, 4 percent had ataxia and 9 percent had mixed spasticity and athetosis; 38 percent had an intelligence quotient (IQ) less than 50, 24 percent between 50 and 79, and 38 percent had IQ above 80. There was a high correlation between overall functional outcome and intellectual level. Severity of physical disability, as measured by hand use, mobility and speech, also correlated with dependence, in part because increased severity of the disability was associated with decreased intellectual capacity generally.

Twenty-five years after the initial visit, parental attitudes and personality intactness were evaluated (using the Minnesota Multiphasic Personality Inventory [MMPI]) and were correlated with satisfaction with status in life in 28 persons predicted to be independent on the 15-year study. Twenty (72 percent) of the 28 were satisfied with their status in life and of these, 16 were evaluated (with the MMPI) with 70 percent scoring in the normal range; 13 (65 percent) had parents with a positive attitude. Positive attitude was defined as parental feelings that the handicapped child was a worthy, valuable person, to be encouraged and assisted but not isolated from the world of nonhandicapped people.

Careful serial assessment by professional teams combined with repeated long-term counseling of families can result in optimal outcome for the disability level involved, due to the primary role parents play in the development of a child's character and behavior.

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*Deceased (December 20, 1977). This paper represents Dr. Peter Cohen's last contribution to the functional and social evaluation of patients with cerebral palsy. As a faculty member in the Department of Pediatrics at the School of Medicine, University of California, San Francisco (UCSF), for 32 years (1942 through 1974), Dr. Cohen estimated that he treated more than 5,000 children with cerebral palsy in addition to many with other developmental disabilities. In 1948 he founded the UCSF Cerebral Palsy Clinic, where he did follow-up studies on these patients over many years. As the first Medical Director (1965 through 1971) of the Golden Gate Regional Center for Developmental Disabilities (GGRC), he was a strong advocate for humane, community treatment of the mentally retarded and other developmentally disabled. After his retirement from UCSF (Professor Emeritus, 1974), he again worked at GGRC until his death.

—JGK

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CEREBRAL PALSY is a syndrome, not a definitive diagnosis;[1,2] the variety of signs and symptoms has made classification and the reliable prediction of outcome in these patients difficult. Bachmann,[3] who studied the variables affecting post-school economic adaptation of orthopedically handicapped students, concluded that vision and hearing handicaps did not seem to affect their future employability but that hand use, mobility and intelligibility of speech played a significant role. We have investigated the functional outcome in a group of such patients in relation to diagnosis and intellectual capability and have attempted

to correlate outcomes with hand use, mobility and speech.

Procedure

The type of cerebral palsy and the intellectual level were noted in 462 patients in whom cerebral palsy was diagnosed at the University of California Cerebral Palsy Clinic in San Francisco from 1949 to 1951 (Table 1). Approximately 15 years later we sent inquiries to the families and requested information on the status of these patients; 319 (67 percent) families replied and, of these, 209 patients returned for reevaluation when they were offered the opportunity. Of the 110 who did not return, 33 (10 percent) had died (Table 2). When the known outcomes were compared with the predictions based on diagnosis (Table 2) or intellectual level (Table 3) they were not substantially different. Since follow-up was done in half or more of the patients in each group, the findings in those whose outcomes were known were considered applicable to the entire group. The questionnaire, returned by 110 patients (or their families), was analyzed for follow-up classification as follows:

- *Independent.* Patients who were married, in a job without concessions or in regular school;
- *Partly dependent.* Those in a job with concessions, a special school or a sheltered workshop, or who were partially supported by family or state funds;
- *Dependent.* Patients in an institution, at home and totally dependent on family, or not employed in any program;
- *Dead.*

For the 209 patients who returned for reevaluation, the judgments on outcome were made after a family interview by a pediatrician, an orthopedist, a psychologist and a social worker (see Table 4).

Physical functional level was evaluated on the basis of hand use, mobility and speech (Figure 1). Disability levels were defined as mild or absent; moderate, when some assistance was required, and severe, when assistance was required for the activities of daily living. Those who returned the questionnaires were evaluated with the use of initial records and written responses.

Psychological tests were given to document the reliability or deviation from the previous testing; these included the Gesell, Stanford-Binet (revised), Wechsler Intelligence Scale for Children and Wechsler Adult Intelligence Scale. Of the 209 patients retested, 26 (12 percent) attained scores that resulted in a change of category from that into which they had been placed originally; 32 (15 percent) scored more than 10 points higher. Twenty-six of these were originally in the category of intelligence quotient (IQ) 80 or above and, therefore, had been eligible for regular

TABLE 2.—*15 Year Outcome of 426 Patients With Cerebral Palsy*

Type of Cerebral Palsy	Initial Visit		Outcome Known: Living		Outcome Known: Dead		Outcome Unknown	
	Number	Percent	Number	Percent	Number	Percent	Number	Percent
Spasticity	235	54	158	55	8	24	87	61
Athetosis	146	32	91	32	21	64	34	24
Ataxia	18	4	11	4	..	..	7	5
Mixed	45	10	26	9	4	12	15	10
TOTAL	462		286		33		143	

TABLE 3.—*IQ Assessment of Patients With Cerebral Palsy*

IQ	Patients Studied 1949-1951		15 Yrs Later Known Alive or Dead		15 Yrs Later Unknown	
	Number	Percent	Number	Percent	Number	Percent
<50	178	38	122	38	56	39
50-79	105	23	75	24	30	21
80+	179	39	122	38	57	40
TOTAL	462		319		143	

TABLE 1.—*Initial Evaluation of 462 Patients With Cerebral Palsy, 1949-1951*

Type of Cerebral Palsy	Number	Percent	IQ<50	IQ 50-79	IQ 80+
Spastic	253	54	..	..	..
Hemiplegia or monoplegia	110	24	25	29	56
Paraplegia, triplegia or quadriplegia	143	30	61	33	49
Athetosis	146	32	67	26	53
Ataxia	18	4	4	6	8
Mixed cerebral palsy	45	10	21	11	13
TOTAL (Percent)	462		178(38)	105(23)	179(39)

school instruction on the basis of the first test. The 52 (25 percent) who scored more than 10 points lower were in the educable and trainable groups; their initial IQ scores were less than 80. Therefore, careful initial testing seemed to be reliable and could have had predictive value in counseling parents.

Results

Intelligence seems to be positively correlated with an outcome that permits independent functioning (Table 4). However, diagnosis of the types of cerebral palsy seemed less strongly associated with outcome if intellectual level is excluded from consideration. This seems to reflect the greater physical disability in the dependent and athetoid groups where intellectual levels are correlated with the three measures of physical function—hand use, mobility and speech (Figure 1).

In general, there is a positive correlation between the severity of physical debility and the degree of mental retardation. This correlates negatively with outcome; that is, the more severe the mental and physical debility, the less likely is a favorable functional outcome. There were two exceptions to these correlations. One was a group of eight patients, with IQ scores of 80 or above and with severe physical disability, who were dependent and were presumed to be so handicapped that their average or higher intellectual capability could not assure independence. The severity of their physical handicaps precluded the use of their mental capability. Another group of eight patients with IQ scores ranging from 50 to 79 and severe physical disability was only partly dependent; four of them were in sheltered workshops, two in special schools and two in jobs with concessions. The implication for this latter group is that the current trends toward more community facilities can increase their competence.

Of the dependent patients with IQ scores less than 50, it was found that 79 percent were severely disabled in one or more physical functions. Of the 143 who were not severely disabled in hand use, mobility or speech, 75 (52 percent) had an IQ of 90 or above and 44 (31 percent) were independent, the largest single independent group (Figure 1).

The psychological evaluation of all the patients with cerebral palsy seems to indicate that measurements of intellectual capacity do not change significantly over the years, especially in the lower ranges (IQ less than 50) and upper ranges (IQ more than 80).

The 48 patients who were predicted to be independent on the basis of the 15 year study (Table 4) were contacted 10 years later, or 25 years after their initial visit. Thirty-four (71 percent) replied to a letter inviting them to return for an interview and further assessment, and twenty-eight (58 percent) were restudied. The remaining six indicated by letter that they were functioning independently in jobs or marriage, or both, but distance prevented their return.

Of the 20 men and 8 women who were reassessed, none were severely disabled and none had

TABLE 4.—*Outcomes of 319 Patients With Cerebral Palsy in Relation to Original Diagnosis and Intelligence Quotient*

	Spasticity					
IQ and Function	*Hemiplegia or Monoplegia*	*Paraplegia, Triplegia Quadriplegia*	*Athetosis*	*Ataxia*	*Mixed*	*Total*
IQ<50						
Independent	..	..	...	..	..	...
Partly Dependent	1	..	1	..	..	2
Dependent	14	36	34	2	13	99
Dead	..	3	16	..	2	21
IQ 50-79						
Independent	1	..	1	..	..	2
Partly Dependent	5	12	7	4	3	31
Dependent	7	15	9	2	3	36
Dead	3	..	2	..	1	6
IQ 80+						
Independent	22	14	7	2	3	48
Partly Dependent	13	16	28	1	1	59
Dependent	1	1	4	..	3	9
Dead	2	..	3	..	1	6
TOTAL	69	97	112	11	30	319

an IQ less than 80. Nineteen of the patients were employed (Table 5) with salaries ranging from $5,000 to $15,000 per year; seven were in school completing college or postgraduate work; two were unemployed. Twenty (71 percent) of the 28 patients were satisfied with their status in life and appeared to have adequate self-confidence and independence; eight felt unsatisfied, unfulfilled and unhappy. The Minnesota Multiphasic Personality Inventory (MMPI) was administered to 23 patients; of the 14 whose scores fell within the normal range, all were satisfied with their present status. A profile of parental attitude was also prepared on each patient, based on history and current evaluation by the team social worker; of the 20 patients who were satisfied with their status in life, 15 had lived in families where the parental attitude was positive or indeterminate, but not negative (Table 6).

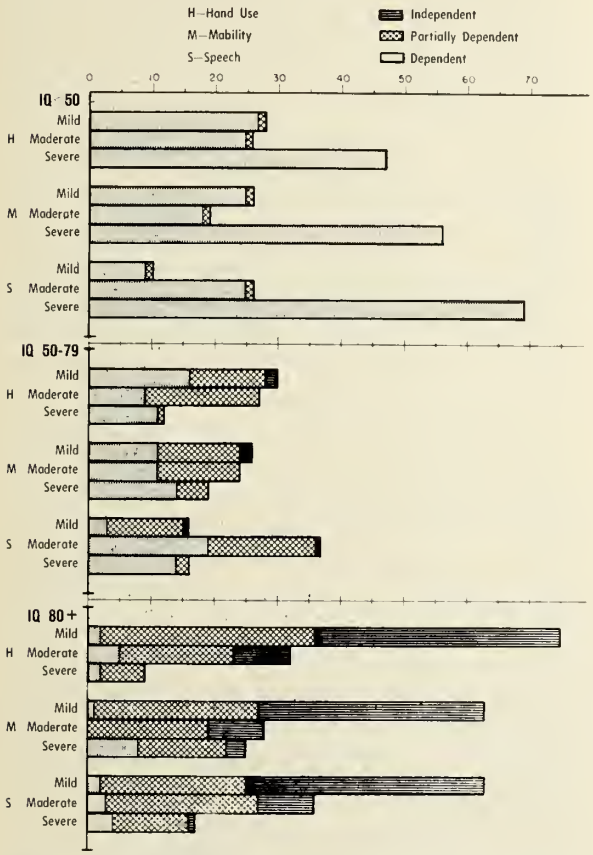

Figure 1.—Outcomes of 286 living patients with cerebral palsy in relation to intelligence quotient and physical function.

TABLE 5.—*Occupations of Adults With Cerebral Palsy—25 Years After Initial Visit*

Auditor, state income tax returns
Bookkeeper
Clerical worker
Computer programmer
Customer service
Finance director of municipality
Foreman, janitorial service
Gate attendant, state park
Janitor
Laboratory technician
Machine cleaner
Postal worker
Saleswoman, home products
Self-employed knitter
Self-employed TV repairman
Supervisor, accounts receivable
Supervisor, workshop
Truck driver, federal works project
Warehouseman

TABLE 6.—*Relation of Present Life Status and Parental Attitude in 28 Patients With Cerebral Palsy*

Correlated with:	*Satisfied*	*Unsatisfied*	*Total*
Parental attitude:			
Positive	13	2	15
Negative	5	5	10
Indeterminate	2	1	3
MMPI:			
Normal	14	0	14
Abnormal	2	7	9
Not done	4	1	5

MMPI = Minnesota Multiphasic Personality Inventory

Positive attitude was defined as parental feelings that the handicapped child be encouraged and assisted, but not kept isolated from other children or adults and not protected from the struggles of growing up in a world of nonhandicapped people—a recognition of the genuine worth of a child with or without handicaps.*

Discussion

The life expectancy of patients with cerebral palsy is shorter than that of normal persons;[4,5] Cohen and Mustacchi[5] found an overall rate eight to nine times expected mortality in a group of 1,416 persons, with a variation from 18-fold to 3-fold with decreasing severity of the defect. Stated in another way, eight of nine patients with cerebral palsy who survive the neonatal period should survive to adult life, with variations in mortality depending upon the severity of the defect. It is the relative longevity of the more mildly disabled patients that has led to the assessment of the quality of life for these people.

There is now a trend away from caring for

*Harriet Johnson, MSW, Doris Ordway, MSW, Elias Katz, PhD, Sylvia Marlowe, Leslie Davison, PhD, and Mrs. Catherine Pietruszewski participated in this study.

handicapped persons in institutions and an increasing emphasis on their living in the community, either with their own families or in small groups. The opportunities the community can and should offer are partly dependent on an estimation of the needs and capabilities of the handicapped.

There have been a number of follow-up studies,[6-12] most of which indicate that individual achievement is related to many factors, such as intelligence, physical function, ability to communicate and personality attributes. The availability of training, jobs, sheltered employment and counseling also contributes to the adjustment of the adults with cerebral palsy. The presence of family or supportive people, financial aid and availability of medical care are further important factors.

Members of the group who might have been predicted as most likely to become independent—that is, those with greater functional physical capacity and higher intellectual ability—did, in fact, become independent in larger numbers than members of other groups. Therefore, it should have been possible to counsel families of these patients after the initial examination and give them an optimistic prognosis. A conclusion regarding limited function could be made about those with severe physical disabilities and lower intellectual capability. Parents should not be encouraged to have unrealistic expectations when all indicators point toward dependency. A comfortable, stimulating environment is very important for those who must lead a largely sheltered existence, but this requires planning and preparation. Parental energies could be better devoted to this task if there is a clear prediction of a child's potential.

A more cautious prognostic approach may be necessary for the middle range of physical disability and intellectual level. Much will depend on available community resources. Parents with children in this group may be well advised to join parent associations that act as advocates for better facilities, training and financial support.

Nielsen[13] suggested that "a large proportion of children with cerebral palsy can be assessed with reasonable accuracy at a relatively early age by commonly applied evaluation methods. Children with neurological and intellectual deficits may be expected to show at least the same, if not a higher degree of IQ stability than nondamaged children." However, members of professional teams who evaluate patients with cerebral palsy should keep in mind the multiplicity of factors involved in management and outcome.

Careful serial assessment combined with long-term counseling of families can result in an optimal outcome for the disability level involved. This is of particular value for the families who suffer from the psychological difficulties of rearing a handicapped child in a culture where physical normality is considered a birthright. Crothers and Paine[10] state that their group of patients, who worked out a satisfactory way of life, insisted on competition. The outstanding asset of that group was the acceptance by their families of the child's disability and not letting disability act as a barrier to the assumption of responsibility. Ingram[1] felt that the subsequent socal lives and employment prospects of patients with cerebral palsy were determined by more than the severity of their physical and intellectual handicaps: factors such as sibling relationships and attitudes of parents were very important. Wortis and Cooper[6] also concluded that factors other than physical played a great role in determining the final outcome. Curtis,[14] a vocational counselor, concluded from his attempts to place a group of adults with cerebral palsy in employment that the single most important factor was the attitude of parents in the very early years of life. Investigators have found it difficult to measure what MacKeith calls "drive" which he described as "the child's innate curiosity and the overall interest with which he interacts with his environment."[15] MacKeith[16] has also written about parental feelings and the way in which these affect their behavior toward the child for whom they are caring.

Smith[17] emphasizes that

> the motivational core of competence is a cluster of attitudes toward self as potent, efficacious and worthy of being taken seriously by one's self and by others. Such a cluster of attitudes sets into motion a kind of self-fulfilling prophecy. In the favorable case, the person has the confidence to seize opportunities as they appear. He tries. He, therefore, acquires the knowledge and skills that make success more probable; this, in turn, validates his sense of efficacy. In the unfavorable case, he does not hope, he does not try—and he is caught in a vicious circle that is likely to mire him in incompetence, fatalism and failure. . . . How to foster the benign sort of circular process and how to break into and disrupt or redirect the vicious sort . . . needs investigation.

From our study, it is apparent that some parents have known how to inculcate positive attitudes in a handicapped child.

Members of professional teams working with parents of handicapped children must recognize the primary role parents play in the development of a child's character and behavior. It appears that this aspect of development is highly significant in the functional outcome of children with cerebral palsy. The challenge is to help more parents to understand and to communicate this attitude in the management of their children with cerebral palsy.

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Accurate Diagnosis and Treatment of Pulmonary Embolism

PULMONARY EMBOLISM . . . is the most commonly missed major medical diagnosis. This was true 10 to 20 years ago and it probably is still true today. In the last few years, however, the emphasis has changed, and it is now fashionable to introduce the topic of pulmonary embolism as being one of the most commonly overdiagnosed medical conditions. My prejudice is that the truth lies somewhere in between, but it is extremely important to accurately establish the diagnosis of of pulmonary embolism. The reason for this is that the mortality rate can be substantially lowered by accurate diagnosis and treatment with anticoagulants, particularly heparin, at the outset. It is also true that the condition should not be overdiagnosed, because of the risk of unjustified anticoagulant therapy. In many drug studies, particularly the cooperative drug analysis system that has been set up in the cooperating hospitals in Boston, it comes out year after year that the drugs that are most commonly associated with serious in-hospital morbidity and even mortality are anticoagulants. So anticoagulants should not be misused and this underscores the need for a reliable diagnosis of pulmonary embolism.

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Arthritis and Hepatitis

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The evidence relating four clinically distinct rheumatologic syndromes to infection by the hepatitis B virus is reviewed. Acute hepatitis B is not infrequently heralded by a prodromal rash and rheumatoidlike polyarthritis. Chronic active hepatitis B more rarely is associated with transient arthritis or arthralgias. Polyarteritis nodosa may be a manifestation of hepatitis B infection in as many as 40 percent of cases, and recently the syndrome of "essential" mixed cryoglobulinemia has also been linked to infection with this virus. The finding of immune complexes of varying composition, sometimes with the viral antigen or its antibody (or both) contained in both the serum and synovial fluid suggests that these four syndromes are clinical manifestations of immune complex disease resulting from hepatitis B infection.

SINCE THE DISCOVERY of Australia antigen as a marker for the serum hepatitis virus in the late 1960's,[1] there has been a resurgence of interest in hepatitis in general and in hepatitis-associated syndromes in particular. With reference to the rheumatic diseases, four syndromes have been described which associate what we now call hepatitis B with rheumatic problems, either arthralgias or frank arthritis. The first is a transient, symmetrical polyarthritis of the rheumatic or rheumatoid type that occurs in the prodromal phase of icteric or anicteric acute hepatitis B.[2-5] In recent years, it has also been observed that a similar type of arthritis can be seen at intervals in chronic active hepatitis.[2] The third is polyarteritis occurring in patients with hepatitis B surface antigenemia.[6] The fourth, and most recently described, is the apparent association with hepatitis B of "essential" mixed cryoglobulinemia,[7] or what had been termed earlier the "purpura, arthralgia, weakness syndrome."[8] In this review we describe the clinical and laboratory features of these syndromes and discuss the possible mechanisms for their pathogenesis.

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Acute Hepatitis B and Arthritis

The first reported association of acute viral hepatitis with arthritis was ostensibly that of Sir Robert Graves in an 1843 textbook in which he made the following observation: "A person laboring under inflammation of the joints gets an attack of hepatitis accompanied by jaundice, and this is followed by urticaria."[9]

Since that time, a number of reports have described discomfort in joints of a transient nature preceding the icteric phase of hepatitis occurring in anywhere from 1 percent to 40 percent of cases. Clinically, the syndrome resembles one-shot serum sickness as induced experimentally by Dixon and co-workers.[10] The symptoms are generally abrupt in onset and consist of low-grade fever, a symmetrical polyarthritis which may be additive or migratory in pattern, morning stiffness and other

ABBREVIATIONS USED IN TEXT

ADCC = antibody-dependent cell-mediated cytotoxicity
anti-HB_sAg = antibody to hepatitis B surface antigen
HB_sAg = hepatitis B surface antigen
PAN = polyarteritis nodosa

constitutional symptoms. The joints most commonly involved are the knees and small joints of the hands. For some reason, the feet are usually spared, but almost any peripheral joint may be involved, with either arthralgia or actual arthritis. In more than 50 percent of cases, a skin rash may accompany or follow shortly after the onset of manifestations in joints. Although usually described as urticarial, this rash may also be erythematous, maculopapular or petechial in nature.

This syndrome may last from several days to several months; in one large series the mean duration was 20 days.[11] Only about 40 percent of the patients ever become jaundiced, in keeping with the accepted incidence of anicteric hepatitis B in general.[4] If jaundice does occur, it may be present initially; more frequently, it develops two to four weeks after the onset of arthritis. The symptoms usually abate with the onset of jaundice or respond quite well to salicylate therapy alone.

It has been observed that when the episode of arthritis is longer in duration, the picture can much resemble rheumatoid arthritis. On occasion, a tentative diagnosis of rheumatoid arthritis has been made until either clinical jaundice or significantly abnormal liver test results have made the correct diagnosis apparent. In each of two reported cases,[5] a nodule histologically resembling a rheumatoid nodule developed; however, the nodule did not recur during follow-up in either case. Typically, the arthritis and rash resolve at about the time that jaundice develops; however, there can be appreciable overlap of these developments, as previously mentioned and as exemplified by Graves's case description.[9] In addition, the patients almost always manifest the more nonspecific symptoms of early viral hepatitis such as malaise, sore throat, anorexia and nausea; but in one large series,[11] it was most often the joint discomfort and rash that motivated the patients to seek medical attention.

There is nothing distinctive about the routine laboratory studies except for the abnormal results of liver enzyme tests. Using a radioimmunoassay technique, Duffy and colleagues[11] found hepatitis B surface antigen (HB_sAg) in the serum of 26 of 29 patients with this syndrome; antibody to HB_sAg (anti-HB_sAg) was found alone in the other three. In none were both antigen and antibody found.

Three patients with hepatitis have been reported,[12] in whom the typical syndrome of rash and polyarthritis was observed but hepatitis-associated antigen could not be found in either serum or synovial fluid. These findings suggested the possibility that the patients had hepatitis A with the typical rheumatic prodrome. However, the sera were sampled only in the icteric or post-icteric phase, when antigen titers are decreasing or may be negative by all but the most sensitive techniques. In other references to infectious hepatitis with arthritis, of pre-Australia-antigen vintage, the diagnosis was made on clinical grounds alone, or was made in cases not associated with injections or transfusions. Since we now know that there can be significant overlap in the incubation periods of hepatitis A and B and that the B virus is not infrequently transmitted by nonparenteral routes, claims for a similar rheumatic syndrome associated with hepatitis A remain unproven, although such a syndrome certainly is possible.

Routine synovianalysis is similarly nonspecific. In one series,[11] leukocyte counts ranged from 465 to 90,000 per cu mm (mean, 24,000 per cu mm), with polymorphonuclear cells predominating in six and mononuclear cells in four. For another patient, there was good viscosity, and the leukocyte count was 7,150 per cu mm, with 75 percent polymorphonuclear cells.[2] However, in another report of three patients,[13] noninflammatory fluid was found (fewer than 2,000 leukocytes per cu mm), as it was in a patient of ours who was seen at the Los Angeles County/University of Southern California Medical Center. The synovial fluid complement levels, however, have almost uniformly been low when studied in the acute phase.[13-15] Concomitant serum levels have also been low in most instances. An interesting inverse relationship between HB_sAg titers and complement component levels has been reported by Alpert and co-workers;[15] in their group of 18 patients, none had detectable antibody to HB_sAg in the serum in the acute phase.

The low serum complement levels, the presence of HB_sAg and the lack of detectable antibody dur-

ing this syndrome are in keeping with the expected pattern of an acute illness that is very like serum sickness.[10] Patients with viral hepatitis who do not have joint or skin symptoms do have normal or increased complement levels. This inverse correlation of antigen and complement suggests consumption of the latter by immune complexes containing HB_sAg; it also suggests that their deposition in synovium might be responsible for the articular symptoms. Earlier work had shown that HB_sAg does induce, in man, formation of an antibody that can form an immune complex and fix complement.[16] Further evidence to support an immune complex pathogenesis for this syndrome includes the finding of HB_sAg by complement fixation techniques in serum and synovial fluid specimens simultaneously obtained in the acute phase,[13] as well as cryoprecipitates containing immune complexes (that is, HB_sAg, IgG, IgM, IgA and complement components C3, C4 and C5). Interestingly, the cryoprecipitates from patients with hepatitis without arthritis contained only HB_sAg, IgG and IgM and were present in lesser concentration than in patients with hepatitis and arthritis.[14] As antigen titers decreased and became undetectable during convalescence, free antibody became detectable in the serum.

Light microscopy examination of a synovial biopsy specimen from a patient with the acute hepatitis B arthritis syndrome showed areas of slight cellular proliferation, vascular congestion and occasional lymphocytes.[2] Electron microscopy revealed 200- to 250-Angstrom round bodies with clear centers in the nuclei of some endothelial cells, and areas of endothelial cytoplasm were replaced by masses of similar particles. These particles are identical to those in liver nuclei of patients with acute hepatitis and have been shown to be the Australia antigen.[19] This suggests that the antigen does reach the synovium, whether by direct invasion or through deposition as part of an immune complex. Duffy and co-workers,[11] however, looked for HB_sAg in synovial fluid of three patients by electron microscopy and found none.

Chronic Active Hepatitis

Joint discomfort and occasional rash have long been mentioned in association with chronic active hepatitis, both with what had been termed lupoid hepatitis[17,18] and in cases associated with chronic or recurrent hepatitis B antigenemia.[20] In chronic active hepatitis, the joint complaints consist mainly of arthralgias of a fleeting nature and perhaps for this reason less investigation into the nature of this syndrome has been done. A recent report describes a case of asymmetrical polyarthritis with erythematous skin lesions in a patient with biopsy-proven, HB_sAg positive chronic active hepatitis.[2] No anti-HB_sAg was found in the serum, as expected, and serum total hemolytic complement was very low. Examination of needle biopsy specimens of involved synovium revealed changes similar to those in the patients with acute hepatitis, including 200-Angstrom particles. Direct immunofluorescence for Australia antigen showed scattered fluorescence throughout the synovium.

A recent study has shed additional light on the possible immune complex pathogenesis of the arthritis associated with chronic active hepatitis B. In a group of ten patients with chronic active hepatitis, three had arthritis and three others had arthralgias while the remaining four had no joint symptoms.[20] Eight of ten had HB_sAg in the serum and in none was anti-HB_sAg found. As in arthritis with acute hepatitis,[14] cryoproteins consisting of IgM, IgG, IgA, C3, C4 and C5 were found during the arthritis phase of chronic active hepatitis in two patients, and HB_sAg was concentrated several-fold in the cryoprotein when compared with serum levels. Since there is convincing evidence that mixed cryoglobulins in the serum represent circulating immune complexes,[21] these findings constitute further evidence pointing to an immune complex pathogenesis for these syndromes. Cryoprotein immune complexes were also found in the serum of three patients with chronic active hepatitis and arthralgias but differed in that only IgG and C5 were found, but no IgM, IgA, C3 or C4. Cryoprecipitable immune complexes were not found in patients with uncomplicated chronic active hepatitis. Antibody to HB_sAg was detected in the cryoprecipitate of one patient.

Polyarteritis Nodosa

The finding of the newly discovered Australia antigen in the serum of patients with a clinical and pathologic syndrome indistinguishable from polyarteritis nodosa (PAN) was described in two articles published in 1970.[6,22] It was then suggested, and has subsequently been shown, that immune complexes containing HB_sAg are present in such patients.[23-26] The incidence of HB_s antigenemia in polyarteritis nodosa has varied depending on the criteria used for diagnosis and the

sensitivity of the technique used for detecting the antigen, but it seems to approach 40 percent.

As reported by Duffy and associates[11] and by Sargent and co-workers,[27] such patients present clinically with the variable multisystem involvement of skin, muscles, nervous system, lungs and kidneys typical of polyarteritis, but in addition they show evidence of liver disease. These two groups of researchers reported on 19 patients with a multisystem disease presenting as polyarteritis and HB_sAg antigenemia. History of drug abuse, exposure to patients with hepatitis or transfusions were notable in some. Most had fever, anemia and leukocytosis. Only three of 19 were jaundiced, but liver test abnormalities were present at some time in 17 of 19. Fourteen had polyarthritis, in some cases resembling rheumatoid arthritis, or arthralgia. Renal disease was present in 14 and was manifested by nephrotic syndrome, lesser proteinuria and microscopic hematuria, hypertension and renal insufficiency. Examination of renal biopsy specimens showed variable degrees of membranoproliferative glomerulonephritis. The typical microaneurysms and small infarcts characteristic of PAN were shown by angiography. Seven of the patients manifested congestive heart failure and three had clinical signs of pericarditis. Additional abnormalities included necrotizing vasculitis with bowel infarction, peripheral neuropathy including mononeuritis multiplex, central nervous system involvement, lower leg ulcerations and nonthrombocytopenic purpura in a few. Seven of the 19 patients died of multisystem or liver disease.

In the sera of 18, HB_sAg was detectable; anti-HB_sAg was detected in sera of three of ten.[11] In many, the antigen was found repeatedly and in others only intermittently over several years. Seven of ten had rheumatoid factor activity in the sera, but none had antinuclear antibodies. Complement levels were low in 13 of 19. Examination of liver biopsy specimens from 16 patients showed a spectrum of changes, ranging from mild periportal infiltration, acute viral hepatitis and chronic persistent or active hepatitis to postnecrotic cirrhosis. In five patients, repeat liver biopsy or autopsy studies showed progression of the histological changes.

Analysis of synovial fluid from six patients[11] showed inflammatory joint fluid with an average leukocyte count of 10,000 per cu mm, usually with a predominance of polymorphonuclear cells. Unlike the situation in acute hepatitis and chronic active hepatitis as outlined previously, complement levels in the synovial fluid were normal. In several cases, HB_sAg was detectable in the synovial fluid.

Ample evidence to substantiate an immune complex pathogenesis for hepatitis B associated polyarteritis nodosa has been presented by several authors.[6,23-26] Immune complexes were detected by various methods: deposition of IgG, IgM, C3 and HB_sAg in arterial walls;[6] passive hemagglutination and density gradient centrifugation;[23] presence of HB_sAg and anti-HB_sAg and demonstration of viral particle aggregates by electron microscopy[11,24,25] and by Raji cell assay and the blocking of antibody-dependent cell-mediated cytotoxicity (ADCC).[26] Some authors suggest that changes in the titer of HB_sAg and anti-HB_sAg and quantity of complexes, measured by these techniques, correlate well with clinical activity of the disease.

Essential Mixed Cryoglobulinemia

Finally, and most recently, an association between what has heretofore been called "essential" mixed cryoglobulinemia and the HB_sAg has been reported.[28,29] This syndrome was first reported in 1966[7] and clinically presents with nonthrombocytopenic-dependent purpura upon exposure to cold, diffuse arthralgias, generalized weakness, hepatosplenomegaly, and occasionally neuropathy and gangrene. In about 50 percent of patients, kidney involvement leads to renal failure in a rather short time. Histologically, an immune complex vasculitis and glomerulonephritis are present, with evidence of IgG, IgM and complement deposition at the sites of tissue damage. The mixed cryoglobulins isolated from the blood in these patients also consist of IgG and IgM, and occasionally IgA and complement components. The IgM may be polyclonal or monoclonal and has rheumatoid factor (antiglobulin) activity. The renal disease, when present, is the usual cause of death.

Presence of cryoproteins has been reported in patients who have positive HB_sAg test results[30] and in others who have the previously mentioned syndromes. However, in "essential" cryoglobulinemia the amount of cryoprotein present is usually greater (from 1 mg per ml up to 5 mg per ml), and symptoms are precipitated upon exposure to cold. Within the past year, Levo and co-workers[29] have reported that 60 percent of

TABLE 1.—*Features of Rheumatic Syndromes Associated With Hepatitis B*

	Acute Hepatitis B	*Chronic Active Hepatitis*	*Polyarteritis Nodosa*	*Mixed Cryoglogulinemia*
Type of joint problem	Transient, symmetrical polyarthritis	Transient, asymmetrical arthritis or arthralgia	Symmetrical polyarthritis in 50 percent	Usually chronic polyarthralgia; arthritis rare
Other systems involved	Skin: evanescent erythematous, urticarial or petechial rash	Erythematous rash rarely reported	Peripheral neuropathy, central nervous system, liver, muscles, skin, intestines, kidneys and heart	Skin (dependent purpura, ulcerations), kidneys, liver, and neuropathy
Hepatitis B surface antigen in serum	Always—during rheumatic prodrome	Variable	Up to 40 percent	Rarely present
Free antibody to hepatitis B surface antigen in serum	Present in convalescent phase	Not present	Rarely present	Present in 48 percent
Leukocytes in synovial fluid	Variable: inflammatory to noninflammatory	Not reported	10,000 per cu mm, polymorphonuclear cells predominant	Not reported
Serum complement	Low	Low	Low	Low with active nephritis
Synovial fluid complement	Low	Not known	Normal	Not known
Immune Complexes	Cryoglobulins (HB_sAg,IgG, IgM,IgA,C3,C4,C5)	Cryoglobulins (HB_sAg,IgG, IgM,IgA,C3,C4,C5)	HB_sAg, anti-HB_sAg	Cryoglobulins (HB_sAg, anti-HB_sAg, complement components)

HB_sAg = hepatitis B surface antigen anti-HB_sAg = antibody to hepatitis B surface antigen

patients who previously would have been classified as having the "purpura arthralgia weakness syndrome" have been shown to have evidence of HB infection. Of the serum specimens from their patients, only 12 percent contained free HB_sAg, but 48 percent had free antibody. Examination of the cryoproteins themselves showed that 74 percent contained either antigen or antibody. Examination by electron microscopy of the cryoprecipitates showed structures resembling the Dane particle of hepatitis B virus. Furthermore, liver involvement in "essential" mixed cryoglobulinemia was clinically or biochemically shown to be present in 84 percent of their patients. Though only a few had overt liver disease, studies of biopsy specimens from a number of patients showed a varying spectrum from minimal change to chronic active hepatitis and cirrhosis. Thus, we now have evidence that in many patients, "essential" mixed cryoglobulinemia is not essential at all but represents yet another syndrome in the spectrum of manifestations of hepatitis B virus infection in man.

Conclusions

Table 1 summarizes some features of the several rheumatic syndromes described in association with hepatitis B virus infection. Why should infection with the same virus produce so varied a clinical response? The answer probably lies in the nature of the immune response of the host to the infection. If we assume that immune complexes do, in fact, mediate at least the rheumatic manifestations of these syndromes, perhaps the size and composition of the complexes formed (class of antibody present, antigen or antibody excess) determine the phenotypic presentation of a single event, that is, infection with hepatitis B virus. This is suggested by the frequent discovery of high titers of free antibody in mixed cryoglobulinemia whereas the free antigen is more often found in polyarteritis and chronic active hepatitis. The cause of polyarteritis and cryoglobulinemia in which no definite evidence of hepatitis B infection can be found remains unknown, but failure to identify it may reflect the insensitivity of our assays for hepatitis B markers. Alternatively other causes, including infection with other viruses, must be considered.

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Addiction to Ophthalmic Corticosteroids

DR. LAIBSON: We must remember, if you can get away without using steroids in any patient with herpes who has never had steroids before, you are far better off to give that a try, because we make our patients with herpes (in many cases) steroid addicts, and they are patients whom you will be seeing for many years to come. So the message is, try to do without steroids if you can, but if you absolutely have to, then in the early stages I would use concomitant antiviral drugs.

DR. THYGESON: We have a dentist, now retired, in Berkeley, California, who was started on a regimen of steroids in 1956 at a second recurrence and he is still receiving steroids, one drop a day. So, he has never had a remission from 1956 to the present. I have 26 such cases in the San Francisco area.

—PETER R. LAIBSON, MD, *Philadelphia*
—PHILLIPS THYGESON, MD, *San Francisco*

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Pneumocystis carinii, Toxoplasma gondii, Cytomegalovirus and the Compromised Host

FRANK W. RYNING, MD, *and* JOHN MILLS, MD, *San Francisco*

Pneumocystis carinii and Toxoplasma gondii are the two major parasitic protozoan pathogens in the immunocompromised host. Both organisms cause latent infection in humans and many animals. Cats are the definitive hosts for toxoplasmosis; the animal vector for pneumocystis (if any) has not been defined. Toxoplasma is an obligate intracellular parasite, whereas the available evidence suggests that Pneumocystis carinii exists primarily extracellularly. In compromised hosts, pneumocystis infection usually involves only lungs, whereas toxoplasma causes a generalized infection with encephalitis being the principal clinical manifestation. Both types of infection are treated with combinations of folate antagonists (trimethoprim or pyrimethamine with sulfonamide). Both parasites are associated with cytomegalovirus infection in immunosuppressed hosts, an association which may be due to symbiosis between parasites, or to an additive immunosuppressive effect of dual infection on the hosts.

IT IS COMMON knowledge that infection is a frequent cause of morbidity and mortality in patients with defective host defenses. Pneumocystis carinii and Toxoplasma gondii are the only protozoa that frequently cause disease in the compromised host. Resistance to infection with these parasites is generally thought to be due to cell-mediated immunity (that is, thymus-derived-lymphocytes [T-lymphocytes] and macrophages), although there is evidence that humoral immunity plays some role in host resistance to infection by both organisms.

Although Pneumocystis and Toxoplasma will be the major focus of this discussion, infection with these two organisms cannot be discussed without reference to cytomegalovirus. This agent is isolated frequently from immunocompromised patients, although many infections are of minimal clinical significance. In addition, dual virus-parasite infections occur frequently, perhaps more commonly than would be expected by chance. At the conclusion of this report, we will examine some of the evidence that infection with one of these organisms, especially cytomegalovirus, may facilitate secondary infection by Pneumocystis carinii or Toxoplasma gondii.

In recent years, the obligate intracellular protozoan Toxoplasma gondii has emerged as a significant pathogen of man and animals. It is one of the most common infections of man. In the United States, approximately 50 percent of the population harbor the latent form of the organism.[1] Most infections in the normal host are asymptomatic, and clinically apparent infections are usually self-limited.[2] In pronounced contrast, toxoplasmosis in the compromised host is frequently fatal.[1]

History

Toxoplasma was discovered in 1908 when Nicolle and Manceaux[3] observed a parasite in

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ABBREVIATIONS USED IN TEXT
IFA = immunofluorescent antibody
SMX = sulfamethoxazole
TMP = trimethoprim

mononuclear cells of a North African rodent, the gondi. The first recognized case of toxoplasmosis in humans was described by Janků in 1923.[4] However, it was not until 1937 that toxoplasmosis as a disease in humans emerged as a potentially serious problem when Wolf and Cowen[5] described a case of congenital infection in a neonate and went on to establish Toxoplasma as a cause of prenatally transmitted human disease. In 1940 Toxoplasma was recognized as a cause of disease in adults when Pinkerton and Weinman[6] described a fatal case in a young man. In 1948 Sabin and Feldman[7] developed a serologic test for the detection of Toxoplasma antibody that greatly facilitated investigation of the epidemiologic and clinical aspects of toxoplasmosis. Although reports describing some of the clinical manifestations of Toxoplasma infection in the normal host appeared first in the 1950's,[8,9] it was not until 1968 that Vietzke and his colleagues[10] at the National Cancer Institute published the first comprehensive study of immunosuppressed patients with toxoplasmosis. These investigators noted a predilection of this organism for the central nervous system and they described the frequent occurrence of concomitant disseminated infection with cytomegalovirus. Finally, it was not until 1969—more than 60 years after the discovery of the parasite—that the cat family was identified as the definitive host of Toxoplasma.[11]

The Organism

Toxoplasma exists in three forms: the trophozoite, the tissue cyst and the oocyst (Figure 1).

The trophozoite (Figures 1A, 1B) of T. gondii is crescentic or oval, approximately 2 μm to 4 μm in width, and 4 μm to 8 μm in length. It is the rapidly proliferating form of the organism seen in tissues during acute infection. The trophozoite can enter all mammalian cells except possibly the nonnucleated erythrocyte.[12] It is easily killed by freezing and thawing, by desiccation and by gastric and duodenal digestive juices.[13] Because it is an obligate intracellular parasite, it does not grow on artificial media but may be propagated in laboratory animals, embryonated eggs and cultured or mammalian cells.

Like most obligate intracellular parasites, T. gondii enters cells by a process called endocytosis whereby the organism is enveloped by host cell pseudopodia that fuse and enclose the parasite within a cytoplasmic vacuole.[14] In the case of cells generally not considered phagocytic, there is controversy concerning the role of the host cell in the entry process.[15] Several investigators have data that they interpret as showing that Toxoplasma can induce phagocytosis in cells such as the fibroblast,[16,17] whereas others have data supporting the view that the parasite is the only active agent in the entry process.[15,18] The controversy remains unresolved.

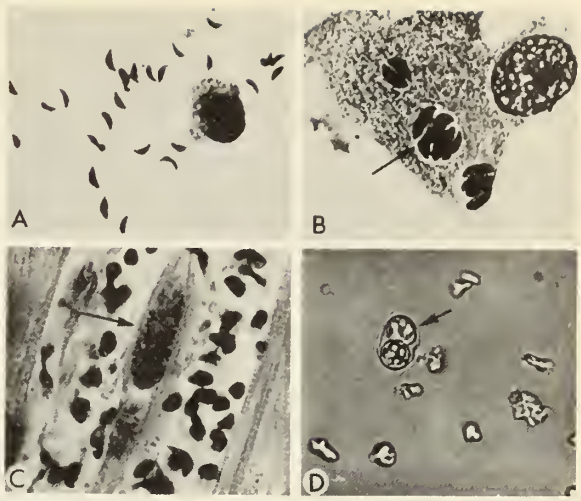

Figure 1.—The three forms of Toxoplasma. **A,** Trophozoites from peritoneal fluid of an infected mouse. **B,** Trophozoites in cytoplasmic vacuoles of human macrophage cultured *in vitro*. Notice that the parasites have replicated, forming a pair, tetrad and rosette **(arrow). C,** Tissue cyst **(arrow)** in human myocardium. **D,** Oocyst **(arrow).** (Reprinted by permission from Anderson S, Remington JS: South Med J 68:1433-1443, Nov 1975.[40])

After cell entry, Toxoplasma undergoes a resting phase and then begins to multiply in cytoplasmic vacuoles, eventually rupturing the cell. Toxoplasma overcomes the microbicidal mechanism of phagocytes, such as macrophages, by preventing lysosomes from fusing with phagosomes in which the parasite resides.[16] The mechanism by which it accomplishes this is not known, but dead Toxoplasma or organisms coated by specific Toxoplasma antibody do not prevent phagolysosome formation and are degraded.[16]

The tissue cyst (Figure 1C) is the latent form of the organism. It is formed by trophozoites within a host cell vacuole. The factors that trigger tissue cyst formation are unknown, but they may be related in part to the development of immunity. Cysts containing viable trophozoites persist in the

host for life.[19] Although tissue cysts are found most commonly in the brain and skeletal and heart muscle, they have been seen in every organ.[19] Cysts evoke minimal host inflammatory response. After ingestion, intestinal proteolytic enzyme and gastric acid exposure disrupts the cyst wall, liberating viable trophozoites within the intestinal tract.[13] Freezing and thawing, heating above 60°C (140°F) and desiccation will destroy tissue cysts.[13]

Oocysts are produced only by members of the cat family, the definitive host of T. gondii (Figure 1D). Oocyst production takes place within the intestinal epithelium. A cat may shed as many as 10^7 oocysts in the feces in a single day,[20] and production of oocysts continues for an average of 14 days.[20] Excreted cysts become infectious only after sporulation, which takes from a day to 21 days depending on environmental factors.[21] As immunity to the intestinal epithelial form of toxoplasmosis in the cat is not complete, production of oocysts can recur after reinfection.[22] The oocyst is the most hardy form of T. gondii; under optimal conditions, it may survive up to a year in soil.

Epidemiology

Worldwide in distribution, toxoplasmosis is one of the most common infections of man. The prevalence of Toxoplasma antibody increases with age, and there is no difference in the prevalence between sexes.[23] Infection occurs naturally in all mammals, some birds, and probably some reptiles.[24] Prevalence of infection varies considerably with geographic location (Table 1). The prevalence of Toxoplasma antibody is higher in the warmer and moister areas of the world than in colder regions.[23] In addition, antibody is more prevalent in populations living at low altitudes than at high altitudes.[25] Toxoplasma infection may be transmitted prenatally or postnatally. Congenital transmission can occur only during infection of a pregnant woman lacking antibody to Toxoplasma.[26] The likelihood of transmission of infection from mother to fetus increases with each trimester of pregnancy; however, clinically apparent disease in the neonate occurs most commonly when the fetus is infected in the first trimester.[27]

TABLE 1.—*Prevalence of Antibodies to Toxoplasma in Different Population Groups**

Population	*Positive Percent*
Iceland	11
Portland, Oregon	17
St. Louis	27
New Orleans	31
Pittsburgh	35
Haiti	36
Honduras	64
Tahiti	68

*Adapted from Feldman and Miller.[23]

Infection acquired after birth is most likely to occur by the oral route. Ingestion of raw or undercooked meat containing tissue cysts is one source of infection; the commercially available meats most likely to contain tissue cysts are lamb and pork.[13] Infection by the oral route also may occur if material is ingested that is contaminated with oocysts from cat feces. The relative role of each of these sources in the overall prevalence of toxoplasmosis in man has not been determined. Several other sources of Toxoplasma infection in humans have been documented (Figure 2). Toxoplasma has been transmitted to seronegative re-

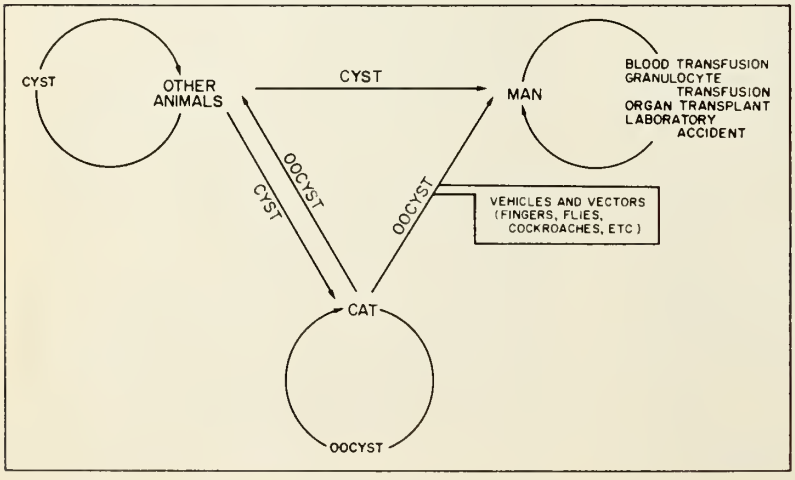

Figure 2.—Transmission of Toxoplasma gondii. (Reprinted by permission from Krick JA, Remington JS: N Engl J Med 298:550-553, Mar 1978.[1])

cipients by transfusion of blood products. In a retrospective study, Siegal and associates[28] documented that transfusion of granulocytes from donors with chronic myelogenous leukemia transmitted Toxoplasma infection to four patients with acute leukemia. Probable transmission of toxoplasmosis by means of organ transplantation has recently been observed (Ryning and co-workers, unpublished observations). In this study, two heart transplant recipients who had no serologic evidence of latent or active Toxoplasma infection at the time of operation developed clinically apparent toxoplasmosis after surgery; one died of disseminated toxoplasmosis and the other survived but had significant neurologic sequelae. Because both heart donors had evidence of recently acquired toxoplasmosis at the time of operation, the transplanted hearts represented the most likely source of infection. Finally, transmission of Toxoplasma infection as a result of laboratory accidents has been described.[29]

Pathogenesis

The walls of ingested oocysts or tissue cysts are degraded by gastric acid and intestinal enzymes. The resulting liberated organisms invade the intestinal epithelium, undergo intracellular multiplication and subsequently disseminate by means of the blood stream to virtually every organ and tissue. Toxoplasma trophozoites invade and destroy host cells, resulting in foci of tissue necrosis that evoke a predominantly mononuclear inflammatory cell response. The host response to infection includes production of antibodies as well as development of cell-mediated immunity. Because intracellular organisms are protected from the lethal effect of antibody and complement,[16] cell-mediated immunity appears to be crucial for the control of Toxoplasma infection as clearly demonstrated in animal experiments.[30] The macrophage is an important component of the effector arm of cell-mediated immunity. Because Toxoplasma can multiply in normal macrophages, effective control of Toxoplasma infection through this arm of the immune response mandates a functional alteration of the macrophage whereby it acquires the ability to kill or inhibit the multiplication of Toxoplasma, a process called macrophage activation. Activation occurs when T-lymphocytes sensitized to Toxoplasma antigen elaborate soluble products called lymphokines in response to Toxoplasma antigen. These lymphokines alter macrophage morphology and function, resulting in activation. The biochemical basis of lymphokine activation of macrophages is largely unknown.

TABLE 2.—*Underlying Conditions Associated With Toxoplasmosis in the Compromised Host**

Underlying Condition	*Percent of Cases*
Malignancies	
Hodgkin disease	40
Non-Hodgkin lymphoma	11
Leukemia	19
Solid	12
Other	2
Collagen-vascular disease	7
Organ transplant	9

*Adapted from Ruskin and Remington.[37]

Clinical Manifestations

Toxoplasmosis may be classified into four categories: (1) congenital, (2) acquired toxoplasmosis in the normal host, (3) acquired or reactivated toxoplasmosis in the immunocompromised host and (4) ocular toxoplasmosis. This discussion will be limited to Toxoplasma in normal and compromised hosts.

Normal Host

Most Toxoplasma infections in the normal host are asymptomatic. Clinical manifestations are usually mild and self-limited, with spontaneous resolution occurring in most cases within one to three months. The most common clinical manifestation is asymptomatic localized lymphadenopathy,[2] which most frequently involves the cervical nodes. Generalized adenopathy can occur. Fluctuation in lymph node size is common and persistence of lymphadenopathy for more than a year has been reported.[31] In addition to lymphadenopathy, various other signs and symptoms such as fever, malaise, pharyngitis and splenomegaly may occur. At times toxoplasmosis may be clinically indistinguishable from infectious mononucleosis caused by Epstein-Barr virus infection. The presence of atypical lymphocytes can add to the confusion.[2] A skin rash may occur; it is generalized, usually nonpruritic, transient and most pronounced on the trunk and proximal extremities.[31] Illness may persist for months, and fluctuations in signs and symptoms are not uncommon.

Clinical illness reflecting isolated organ involvement in the normal host has been described but is uncommon. Myocarditis secondary to de-

struction of myocardial cells by trophozoites may cause serious consequences.[31] Pericarditis may occur but is rare.[32] Toxoplasma has been implicated as a cause of pneumonia,[33] myositis,[34] and hepatitis with a clinical course and liver enzyme rise similar to that of viral hepatitis.[35] Toxoplasma-induced encephalitis in the normal host is rare. Chorioretinitis due to Toxoplasma has been observed in the normal host during the course of acquired infection, but most cases probably represent activation of congenitally acquired disease.[36]

Compromised Host

Toxoplasma gondii has emerged as an important opportunistic pathogen in the compromised host that is capable of producing rapidly fatal disseminated infection. Sources of infection in this setting include reactivation of latent infection during immunosuppression and introduction of organisms into a host with impaired immunologic mechanisms.

Toxoplasmosis in the compromised host occurs most frequently in patients with lymphoreticular malignancies, particularly Hodgkin disease, but it has been associated with a wide variety of underlying conditions including hematologic malignancies, solid tumors, collagen-vascular disease and organ transplantation (Table 2).[37] It is unusual for toxoplasmosis to occur unless the patient is receiving immunosuppressive therapy.[37]

In the compromised host, the central nervous system is the most common site of involvement. There is evidence of meningoencephalitis in more than 90 percent of immunosuppressed patients with toxoplasmosis.[1] The neurologic signs and symptoms are nonspecific (Table 3), reflecting diffuse or focal involvement. The most common manifestation is alteration of mental status. Mass lesions may occur, mimicking a brain abscess.[38] The cerebrospinal fluid abnormalities also are nonspecific. Typical findings include mild pleocytosis with a predominance of mononuclear cells, a normal glucose level and mild-to-moderate elevations in protein concentration. Although Toxoplasma has a predilection for the central nervous system, virtually any organ system can be involved. Necrotizing myocarditis and interstitial pneumonia are not uncommon.[1] Manifestations of Toxoplasma infection such as lymphadenopathy or hepatosplenomegaly that are common in the normal host also may occur in the immunocompromised patient. Persistent fever, unresponsive to antibiotics, may be the initial manifestation of Toxoplasma infection.[39] Unfortunately, the manifestations of Toxoplasma infection in the compromised host are nonspecific and similar to those that may be produced by the patient's underlying disease or other opportunistic pathogens.

TABLE 3.—*Neurologic Signs and Symptoms of Toxoplasmosis in the Compromised Host**

Signs or Symptoms	*Percent*
Alteration of mental status	68
Motor impairment	32
Seizures	24
Abnormal reflexes	16
Headache	14
Vomiting (projectile)	5
Sensory impairment	5

*Adapted from Remington.[2]

Diagnosis

The diagnosis of acute toxoplasmosis can be made by (1) serologic tests, (2) histologic examination of infected tissue and (3) isolation of the parasite.

Serologic Testing

Serologic tests for the detection of Toxoplasma antibody constitute the primary mechanism of diagnosis of acute and chronic infection. The humoral response to Toxoplasma infection usually includes production of both IgG and IgM antibodies. IgM antibodies are detected using the immunofluorescent antibody (IFA) technique. The usefulness of this test is based on the observation that IgM antibodies appear before IgG antibodies and persist for only a relatively brief period in most patients. The test was originally designed to facilitate the diagnosis of congenital infection by differentiating passively transferred antibody (IgG) from the infant's own IgM antibody response. However, it is also quite useful in the diagnosis of acute infection in the normal and compromised host.

IgM antibodies usually appear during the first week of infection, rise rapidly, peak within the first month, and then decline and disappear three or four months after onset of the infection. In some cases IgM antibody may disappear as early as three weeks after infection.[1] During acute infection, IgM Toxoplasma titers can vary widely from 1:10 to greater than 1:1,000, but only a fourfold or greater rise or an extremely high titer (1:160 or higher) establishes the presence of acute infection.[40] A low titer does not exclude the

possibility of active infection.[40] Although in most cases IgM antibodies disappear within three to four months, in some cases IgM antibodies have persisted for months or even years but usually at low titers of 1:20 or less.

IgG antibodies may be detected by IFA (the test most commonly used), the Sabin-Feldman dye test, indirect hemagglutination, or complement fixation. As with the IgM-IFA test, a fourfold rise in IgG antibody titers between serum samples run in parallel establishes the diagnosis of acute infection.[40] Titers measured by these tests rise more slowly than IgM titers, at times taking two months or more to peak.[1] In most cases, the maximum titer usually exceeds 1:1,000, and titers of 1:10,000 and higher have been reported.[1] Because high titers of IgG antibody have been known to persist for years, an isolated high titer does not establish the presence of acute infection.[1] After four to six months, the IgG titer slowly begins to fall, but usually some antibody remains indefinitely.[40] Treatment may blunt maximal antibody response if it is begun early enough; however, once maximal levels are reached, treatment rarely has an effect.[27] Complement-fixing and hemagglutinating antibodies usually develop later and rise more slowly than IgG-IFA or dye test antibodies.[40]

Histologic Diagnosis

A definitive diagnosis of acute toxoplasmosis can be made by the demonstration of trophozoites in tissues or body fluids.[40] The recognition of trophozoites in histologic sections is difficult but can be facilitated by using Giemsa or Wright stain rather than hematoxylin and eosin. Immunofluorescent staining also may facilitate identification of organisms.[41] The presence of cysts in tissue usually represents subacute or chronic infections; but, because these structures can form early, their presence does not exclude the possibility of acute infection. Lymph node architecture during Toxoplasma lymphadenitis is sufficiently characteristic to be considered diagnostic.[42]

Isolation

Isolation of the organism from body fluids (for example, cerebrospinal fluid or aqueous humor) establishes the diagnosis of acute Toxoplasma infection. This is usually accomplished by injecting suspect fluids into the peritoneal cavity of a mouse. Use of this method frequently delays establishing the diagnosis. Because the organisms can be recovered from tissues containing cysts, their isolation from this source does not necessarily indicate acute infection.

Summary—Diagnosis

Normal Host

The methods most commonly employed in the diagnosis of acute Toxoplasma infection in the normal host are summarized in Table 4. The demonstration of a fourfold rise of IgM or IgG antibodies or the presence of an extremely high IgM titer (excluding false-positive results due to the presence of rheumatoid factor and antinuclear antibody) establishes the diagnosis of acute infection. Histologic examination of a lymph node

TABLE 4.—*Guide to the Diagnosis of Toxoplasmosis**

Syndrome	*Definitive Diagnosis*	*Presumptive Diagnosis*
Acute acquired toxoplasmosis in the immunocompetent host	1. Rising antibody titer 2. Markedly elevated titers of IgM-IFA ($\geq$1:160) in presence or absence of symptoms 3. Characteristic histology on lymph node biopsy	1. Elevated titer of DT or IFA ($\geq$1:1,000) and positive IgM-IFA test associated with characteristic clinical syndrome (for example, lymphadenopathy, "mononucleosis-like" syndrome)
Acute toxoplasmosis in the immunodeficient host	1. Rising antibody titer 2. Markedly elevated titers of IgM-IFA ($\geq$1:160) 3. DT titer per IgG concentration greater in cerebrospinal fluid than in serum 4. Histologic or cytologic demonstration of trophozoite (for example, brain or lung biopsy, bone marrow aspirate, cerebrospinal fluid sediment) 5. Isolation of parasite from cerebrospinal fluid	1. Elevated titer of DT, IFA, CF, IHA, or IgM-IFA associated with characteristic clinical syndrome (for example, encephalitis, pneumonitis, myocarditis, lymphadenopathy)

CF = complement fixing antibody
DT = Sabin-Feldman dye test antibody
IFA = immunofluorescent antibody
IHA = indirect hemagglutinating antibody

*Adapted from Anderson and Remington.[40]

also can secure the diagnosis. A presumptive diagnosis of acute Toxoplasma infection may be made in the presence of an elevated IgG titer (1:1,000 or higher) and a positive IgM-IFA test associated with characteristic clinical manifestations.

Compromised Host

The criteria for the definitive and presumptive diagnosis of acute toxoplasmosis in the compromised host also are summarized in Table 4. The same serologic criteria for the definitive diagnosis of acute toxoplasmosis in the normal host apply to the compromised host. False-negative serologic tests may occur.[1] Although not frequently used, the demonstration of local central nervous system antibody production by finding a greater Toxoplasma IgG titer per gram of globulin in cerebrospinal fluid than in the serum is diagnostic of active infection. Finally, isolation of trophozoites from body fluids also is definitive proof of infection.

Treatment

Sulfadiazine or triple sulfonamides combined with pyrimethamine is the standard treatment regimen for toxoplasmosis. Both drugs are used because the combination is synergistic against Toxoplasma.[43] Therapy in the normal host is usually not necessary because of the self-limited nature of the infection but is indicated when vital organs are infected or severe constitutional symptoms persist.[1]

In the compromised host, therapy is always indicated because most patients will die if they are not treated.[37] Retrospective studies have shown an 80 percent response rate if therapy with sulfadiazine and pyrimethamine is instituted early in the course of the illness.[37] Toxicity can occur with these drugs. The side effects of the sulfonamides are well known; pyrimethamine may cause bone marrow suppression, but the risk can be minimized by the administration of folinic acid and fresh yeast.

Prevention

An important aspect of the control of Toxoplasma infection is the prevention of infection in the compromised host. Meat should be stored at −20°C (−4°F) or heated to 60°C (140°F) for 15 minutes to kill tissue cysts. Hands should be washed before eating and after touching uncooked meat. Cat feces or material potentially contaminated by cat feces should be avoided. Periodic serologic testing is extremely important to facilitate the diagnosis of Toxoplasma infection. Because this organism can be transmitted by means of blood, blood products or transplanted organs, it may be prudent to use seronegative donors.

Dual Infections

There has been ample documentation of concomitant infection with Toxoplasma and cytomegalovirus in the compromised host.[44,45] In 1956 Hemsath and Pinkerton[46] described simultaneous disseminated cytomegalic inclusion disease and toxoplasmosis in an adult with myeloid metaplasia. In 1968 Vietzke and colleagues[10] at the National Cancer Institute were the first to call attention to the striking concurrence of disseminated cytomegalovirus and Toxoplasma infection in patients with altered host defenses. They suggested that this association might be more than a fortuitous occurrence and that there might be a symbiotic relationship. Individual human cells infected with both organisms also have been observed.[10] This association is discussed more fully at the end of this report.

Pneumocystis Carinii

Pneumocystis carinii is an organism that has not been classified definitely, although it is commonly believed to be a protozoan. In 1909 Chagas[47] in Brazil first observed the organism in the lungs of guinea pigs experimentally infected with Trypanosoma cruzi. He later saw similar parasites in the lungs of a man dying of American trypanosomiasis.[48] Carini, also working in Brazil, found similar organisms in the lungs of rats experimentally infected with trypanosomes; both investigators thought they were specialized forms of trypanosomes.[49] In 1912 Madame and Monsieur Delanöe[50] reviewed Carini's slides and realized that they had observed this organism in the lungs of Parisian sewer rats not infected with other protozoans, thereby distinguishing it as a separate parasite. They named the organism Pneumocystis carinii to indicate its apparent tissue tropism and to honor one of its discoverers. At that time, no animal or human disease was attributed to this parasite.

In the early years of World War II, two German physicians, Ammich[51] and Beneke,[52] described a nonsyphilitic interstitial plasma cell

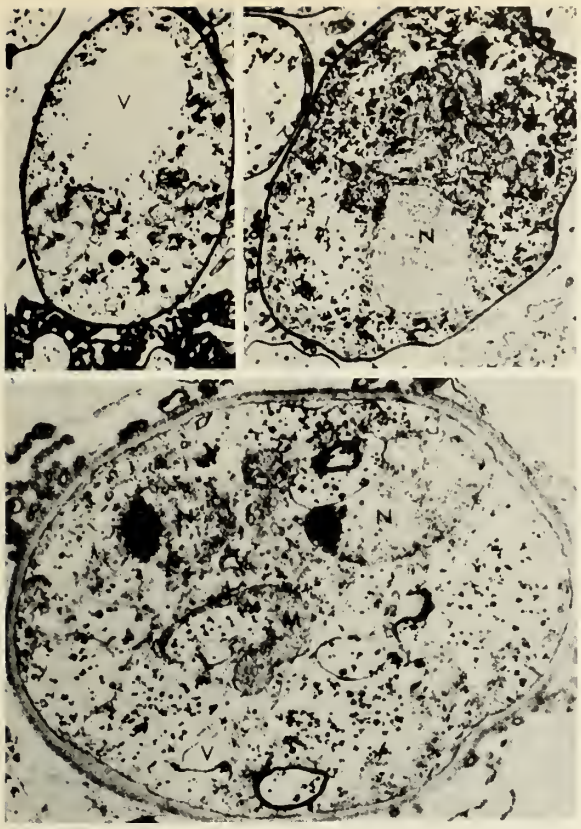

Figure 3.—Electron micrographs of Pneumocystis carinii in infected rat lung, stained with lead citrate. **Top:** Trophozoites with early thickening of surface pellicle, vacuole (V), nucleus (N) and numerous mitochondria (×15,000-21,000). **Bottom:** Cyst with fully-developed trilaminar wall. Nuclei (N), mitochondria (M) and vacuoles (V) can be seen (×37,000). (Reprinted by permission from Barton EG Jr, Campbell WG Jr: Am J Pathol 54:209-236, Feb 1969.[61])

pneumonia in human neonates and infants. This illness assumed epidemic proportions in Europe during the years of World War II, especially among malnourished infants in foundling homes.[53] Although Ammich, Beneke and subsequent investigators during the war years were not able to implicate an etiologic agent in this illness, review of their published photomicrographs has shown the presence of P. carinii. In 1942 two Dutch investigators, Van de Meer and Brug,[54] found P. carinii in the lungs of three patients post mortem, although there was no associated clinical illness or inflammatory response. It was not until 1951 that a Czechoslovakian worker, Vanêk,[55,56] solidly associated P. carinii infection with plasma cell pneumonia of children. His work was widely discounted in the United States, however, and it was not until several years later that the Nobel laureate D. Carleton Gajdusek lent his influence to this observation,[57] and P. carinii became accepted as the principal etiologic agent of interstitial plasma cell pneumonia in infants and children. In 1955, Hutchison[58] reported an association between P. carinii pneumonia and congenital immunodeficiency. Pentamidine isethionate was first used for treatment in 1963,[59] but related aromatic diamidines were used as early as 1957.[60]

The Organism

What sort of organism is P. carinii? Because it has only recently been grown *in vitro,* all of the evidence to date that we have about its structure and life cycle derives from morphologic observations on organisms grown in animal lungs. Barton and Campbell[61] have published the definitive work on the electron microscopic morphology of this organism in rats, and similar observations have been made on material from human lungs.[62] Two forms can be distinguished, the trophozoite and the cyst, with intermediate forms suggesting that trophozoites develop into cysts containing four to eight trophozoites. Fully developed cysts apparently rupture and release trophozoites into the surrounding environment. Based on electron microscopic observations of infected rat lungs, Vossen and co-workers[63] suggested that partially developed cysts also may release trophozoites. Figure 3, from Barton and Campbell's studies, shows trophozoite forms in the two top panels. They contain intracytoplasmic organelles typical of eukaryotic cells, such as a nucleus, endoplasmic reticulum and mitochondria. An early cyst form is shown in the lower panel, and in Figure 4 a mature cyst form is shown, with four trophozoites contained within it. Morphologically, the trophozoites resemble those of T. gondii, except that Pneumocystis trophozoites lack specialized polar structures thought to be used for cell entry.

The available evidence strongly supports inclusion of P. carinii in the phylum Protozoa, probably in the class Sporozoa.[64] In experimental animals, infection with this organism responds to antiprotozoal drugs such as the aromatic diamadines and folate antagonists and does not respond to antifungal agents such as amphotericin B or to antibiotics.[65] The organism does not grow on acellular media that support the growth of most fungi and bacteria,[66] and it has a broad host range similar to that of Toxoplasma.[64] The electron microscope shows intracellular organelles similar to those found in eukaryotic cells and not found

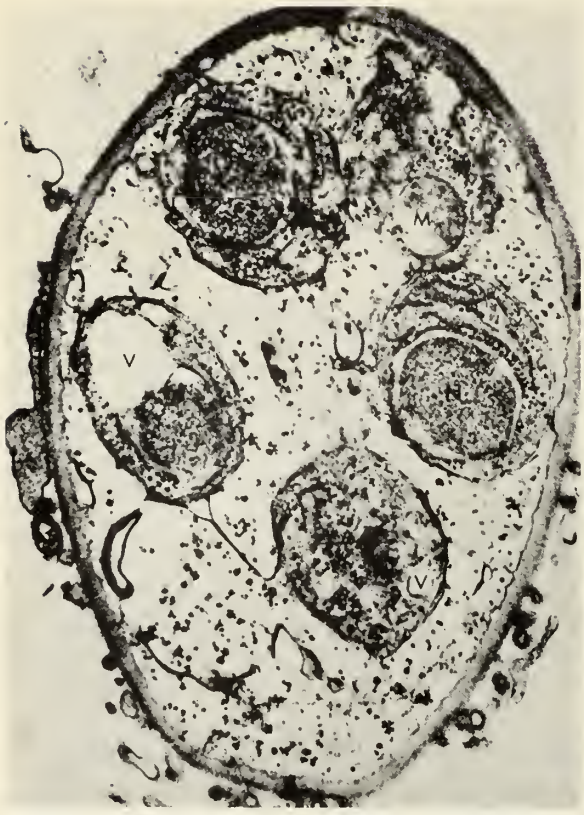

Figure 4.—Electron micrograph of fully developed cyst of Pneumocystis carinii from infected rat lung, stained with lead citrate. Five intracystic bodies (? immature trophozoites) are seen. Mitochondria (M), nuclei (N) and cytoplasmic vacuoles (V) are seen (×50,000). (Reprinted by permission from Barton EG Jr, Campbell WG Jr: Am J Pathol 54:209-236, Feb 1969.[61])

in prokaryocytes such as fungi and bacteria.[61-63] Now that the organism has been grown *in vitro*[66-68] it seems likely that metabolic studies will be done to precisely define its taxonomic status.

Epidemiology

Pneumocystis has been found in all geographic locations where an effort has been made to find it.[69] It has an extraordinarily wide host range: it has been demonstrated in the lungs of many higher primates; a number of domestic animals, including horses, sheep, goats, pigs, dogs and cats; some wild animals, such as foxes, and a number of rodent species, including rats, guinea pigs, mice and rabbits.[64] Although most of these observations have been incidental ones, without associated disease in the host, there are a few reports of clinically significant Pneumocystis pneumonia in animals. For example, a recent case report in the *Journal of the American Veterinary Association* describes two cases of fatal Pneumocystis pneumonia in Arabian colts.[70]

Because the lung is the major target organ of this parasite, one would expect the major route of infection to be aerosol transmission, and this has been confirmed in a number of animal experiments.[71] However, there is no direct evidence as to the mechanism of spread to or among humans. In addition, it is not clear whether human disease is due to primary infection or to reactivation of a latent infection. Although some clinical case reports suggest possible human-to-human transmission (primarily nosocomial) with disease resulting from primary infection,[72] the weight of the evidence presently available clearly favors reactivation in the majority of patients with pneumocystosis. Many strains of rats (and also other rodents) are asymptomatic carriers of P. carinii, and immunosuppression in these animals results in 100 percent mortality from Pneumocystis pneumonitis.[65] In humans, the incidence of Pneumocystis pneumonitis is directly proportional to the intensity of immunosuppressive therapy, suggesting reactivation of latent infection as the primary cause of disease.[73] Finally, recent data from Holland and the United States, using an immunofluorescent assay for antibody to P. carinii, suggest that infection is widespread and occurs early in life (Figure 5).[74-77] By the age of four years, the prevalence of antibody to P. carinii is 75 percent to 80 percent, and it remains at this level throughout life. These data suggest that, as in the other animal species studied so far, human infection with Pneumocystis is widespread and that disease results from reactivation of latent infection when host defenses are compromised by immunosuppressive agents or other factors.

Predisposing Conditions

What are the clinical conditions that are associated with P. carinii pneumonitis in humans (Table 5)? Historically, it has been associated with prematurity and starvation or malnutrition in children.[53,57,59] The disease was described subsequently in patients with congenital immunodeficiency of either the humoral or cellular type.[78] More recently, it has been reported in adults with acquired immunodeficiency, either due to disease or drug therapy.[79,80] Because there are data now to support the notion that both prematurity and starvation are associated with defects in cell-mediated and humoral immunity,[81] we may assume that the common denominator of P. carinii infection is immunodeficiency. Although most of the conditions associated with clinical pneumo-

cytosis appear to be defects predominantly of cell-mediated immune function, there are well-described cases in children with isolated humoral immunodeficiency, in whom cellular immunity has been shown to be normal by all of the presently available tests.[69] The disease is extremely rare in otherwise healthy persons.[82]

The clinical association between pneumocystosis and starvation is solidly established and can be reproduced in the rat model mentioned previously (Figure 6).[83] Normal rats given either a regular or a low-protein diet continue to gain weight and show little evidence of pneumocystosis post mortem. In contrast, when rats are fed a protein-free diet, which produces weight loss and hypoalbuminemia, virtually all develop fatal pneumocystosis.

Treatment with corticosteroids has been a regular predisposing factor in most series of patients with P. carinii pneumonitis without prematurity, malnutrition or congenital immunodeficiency as an underlying factor.[69,72,79,80,84] This apparent selective ability of corticosteroids to induce P. carinii pneumonitis in patients is substantiated by the data of Frenkel and associates in the rat model, as he was able to induce P. carinii pneumonitis only with corticosteroids or cyclophosphamide (Cytoxan).[65] Total body irradiation, lymphoid ablation, methotrexate, chlorambucil, nitrogen mustard, 6-mercaptopurine and vinblastine did not induce pneumocystosis when used alone.

Recent studies by Masur and Jones[89] at Cornell may have defined a role for humoral antibody in resistance to P. carinii infection. When monolayer cultures of rat alveolar macrophages were exposed to Pneumocystis organisms obtained by lung lavage, the organisms attached to the outside of the macrophage cell envelope and remained there in a stable state for as long as several days. If antibody to Pneumocystis was added to the monolayer cultures, the attached parasites were rapidly phagocytosed and digested. Morphologically intact intracellular organisms were not observed, suggesting that P. carinii is not a facultative intracellular parasite. Antibody (with or without complement) added to Pneumocystis organisms in the absence of phagocytic cells had no apparent effect on the organisms; thus, antibody may act as an opsonizing agent essential to destruction of this organism by phagocytic cells. The role of other immune factors in resistance to Pneumocystis, such as thymus-dependent lymphocytes, cytotoxic lymphocytes or activated macrophages, remains to be defined. The recent development of the nude mouse as a model for P. carinii infection may allow further studies on the nature of immunity to Pneumocystis.[90]

TABLE 5.—*Conditions Predisposing to Pneumocystosis*

Prematurity
Starvation/malnutrition
Congenital immunodeficiency
Humoral
Cellular
Acquired immunodeficiency
Lymphoid malignancy
Drugs (especially corticosteroids)

Clinical Features

In the United States, the usual clinical features of a patient with P. carinii pneumonitis are those of an immunocompromised host who develops nonproductive cough, dyspnea (often with cyanosis as the disease progresses), respiratory distress, pulmonary infiltrates and hypoxia.[69,79,80,84-88] As mentioned previously, most patients with pneumocystosis have been receiving immunosuppressive drug therapy, particularly corticosteroids.[73,79,84,85,88] In the clinical studies that have

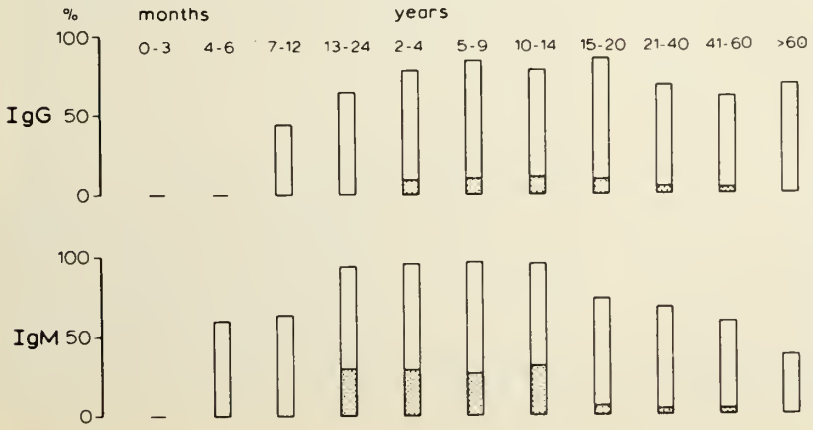

Figure 5.—Age distribution of IgG and IgM antibodies to Pneumocystis carinii in normal children, as determined by indirect immunofluorescence. Percentage of children with titers of 1:40 or higher (open bars) and 1:160 or higher (shaded bars) is shown. (Reprinted by permission from The University of Chicago Press and Meuwissen JHETh, Tauber I, Leeuwenberg ADEM, et al: J Infect Dis 136:43-45, Jul 1977.[74])

been reported, approximately 60 percent of the patients with corticosteroid-associated pneumocystosis have had their corticosteroid dosage reduced or discontinued shortly before the onset of significant pneumocystosis.[69,72,79,88] Virtually all patients have cough and dyspnea; hypoxia (arterial oxygen pressure of 80 mm of mercury or less while breathing room air) and hypocarbia also were present in most patients.[69,79,80,84,87] Hypercarbia may occur as the illness progresses. Pulmonary infiltrates tend to be symmetric and predominantly perihilar at first, with an interstitial and alveolar pattern. Later, extensive pulmonary consolidation with air bronchograms may be seen.[69,84-87] Atypical roentgenographic findings may occur; and patients with lobar consolidations, coin lesions and normal chest roentgenograms have been described.[91,92] The onset of illness is variable: it is more commonly acute with the patient progressing to severe respiratory failure over the space of two to ten days, but patients with a subacute or chronic evolution have been described.[84,86] Only half of the patients have fever, making this an unreliable sign of pneumocystosis.[84-87] The leukocyte count is not helpful, although lymphopenia or eosinophilia (or both) have been noted in some patients.[79] In the immunocompromised patient, death is usual if specific chemotherapy is not administered.

Although virtually all patients with pneumocystosis have disease confined to the lung, metastatic infection has been reported in a small number of cases.[93-96] When dissemination occurs, the organisms are found predominantly in regional lymph nodes (for example, perihilar nodes);[93] dissemination to more distant lymphoid tissues such as the spleen, liver and other lymph nodes is uncommon. Only rarely has P. carinii been found in tissues other than the lung and reticuloendothelial system.[94,96] Congenital infection can occur but is uncommon.[69] Multiple episodes of pneumocystosis have been described in individual patients; these probably represent relapses rather than recurrent infections.[85,97] Several instances of interstitial fibrosis occurring subsequent to P. carinii pneumonitis have been reported.[98] However, because interstitial fibrosis has occurred in patients with lymphoid malignancies and in patients receiving immunosuppressive therapy without P. carinii pneumonitis, it is premature to ascribe an etiologic relationship between Pneumocystis infection and subsequent interstitial fibrosis.

Dual Infections

Dual infections with cytomegalovirus were noted in the earliest clinical series of immunosuppressed patients with P. carinii pneumonitis.[73] The frequency of dual infections depends on the patient population studied (Table 6). In several series of patients with renal transplants, the incidence of coexisting cytomegalovirus infection in patients with pneumocystosis was quite high;[79,85] however, it has not been proved to be significantly higher than the incidence of cytomegalovirus infection in the transplant population overall. In other series of patients with tissue transplants or

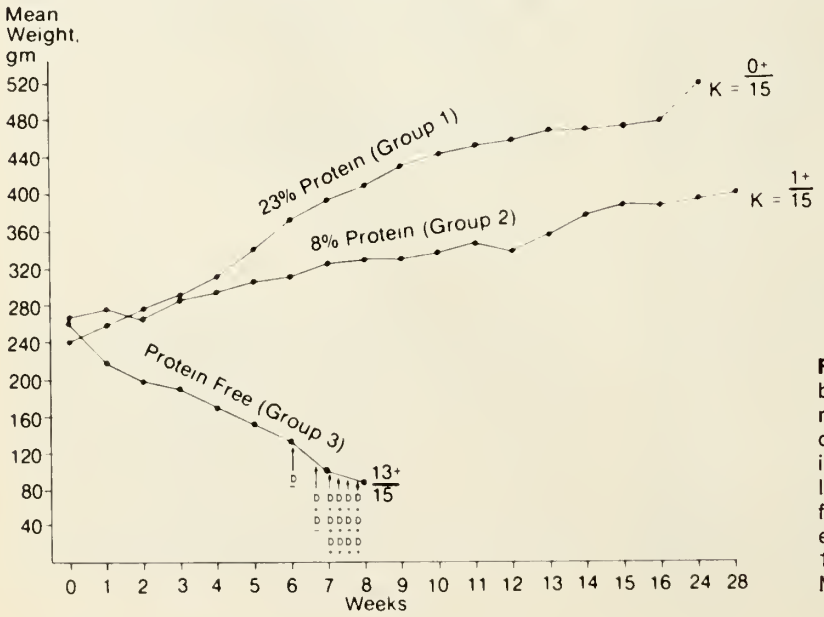

Figure 6.—Effects of various diets on body weights and incidence of Pneumocystosis in rats. Spontaneous death (D), killed (K), P, carinii found in lungs (+), P. carinii not found in lungs (−). (Reprinted by permission from Hughes WT, Price RA, Sisko F, et al: Am J Dis Child 128:44-52, Jul 1974;[83] copyright 1974, American Medical Association.)

TABLE 6.—*Clinical Association Between Pneumocystosis and Cytomegalovirus Infection*

Type of Patients	*Reference Number*	*Number of Patients*	*Percent Incidence of CMV in Patients with PC*
Renal transplants	114	7	71
Renal transplants	79	10	70
Transplants and malignancies	85	24	21
Transplants and malignancies	115	14	20
Malignancies	87	20	40
Malignancies	84	7	14
Malignancies (children)	80	51	10
Malignancies (children)	104	18	0

PC = pneumocystosis
CMV = cytomegalovirus

TABLE 7.—*Open Lung Biopsy in Diagnosis of Pulmonary Infiltrates in the Compromised Host (47 Patients)**

Item	*Percent of Patients*
Operative complications	0
Pneumocystosis, total	35
Alone	23
Other diseases	62
Pneumonia (idiopathic)	29
Tumor	10
Fungal infection	10
Bacterial infection	8
Other	13

*Adapted from Rosen et al.[87]

lymphoid and hematologic malignancies, the incidence of cytomegalovirus infection apparently was somewhat lower, although its presence was not always excluded rigorously.[80,87] A 33 percent incidence of antibody to P. carinii in immunocompromised patients with cytomegalovirus infection as reported by Norman and Kagan[75,76] suggests a relatively high frequency of dual infection overall. As will be discussed subsequently, there may be good explanations for why cytomegalovirus infection facilitates the subsequent development of Pneumocystis pneumonia.

Diagnosis

Making the diagnosis of P. carinii pneumonitis is part of the larger question of diagnosing the cause of pulmonary infiltrates in the immunocompromised host. The diagnosis of pneumocystosis rests on morphologic identification of the organism in tissues and secretions. This can be achieved using a variety of stains. Toluidine blue O, methylene blue and Gomori's methenamine silver stains have proved most satisfactory for demonstration of cysts and Giemsa stain for trophozoites.[69,99] Transtracheal aspirates reveal P. carinii in only 5 percent to 10 percent of patients with disease.[85,100] Bronchopulmonary lavage, either using a bronchoscope or a Carlen's catheter, has been used successfully to obtain P. carinii in some instances, although insufficient numbers of patients have been studied comparatively to determine the precise yield of this procedure.[101] Similarly, bronchial brushings have been successful in some instances, but usually the yield is not high and the material obtained contains artifacts that are difficult to distinguish from Pneumocystis cysts.[102] Needle aspiration of the lung has been used extensively and appears to produce an 80 percent to 90 percent yield with low complication rate.[80,85,100] Needle biopsy is an effective procedure for making the diagnosis, but because the rate of complications has been excessively high this procedure generally has been abandoned.[85] Therefore, when pulmonary tissue is required for histologic examination, either transbronchoscopic or open lung biopsy is utilized. Few studies have compared these two biopsy procedures in patients with pneumocystosis. However, bronchoscopic biopsy appears to be 80 per-percent or 90 percent as sensitive as open lung biopsy, although a recent report suggests it is even less sensitive.[103] Open lung biopsy is the diagnostic procedure by which other procedures are judged, but there are occasional reports of cases of pneumocystosis or other infections that have been missed even by open lung biopsy.[103]

Recently, investigators at Memorial Sloan-Kettering Cancer Center reported their experience with open lung biopsy in the diagnosis of pneumocystosis and other pulmonary infiltrates in the compromised host (Table 7).[104] Open lung biopsy studies were done in 47 patients with only a negligible rate of operative complications,[104] which has been the experience at other centers including the University of California, San Francisco. A third of the patients had P. carinii pneumonitis, and approximately two thirds of these had no other pulmonary abnormalities. Another 20 percent of the patients had either bacterial or fungal infections. Thus, over half of the patients had some sort of pulmonary infection, and it is likely that most of these would have been diagnosed by needle aspiration. On the other hand, nearly a third of the patients had idiopathic interstitial pneumonia without an associated infection, and an additional 23 percent had pulmonary tumor or other conditions, such as drug-induced pul-

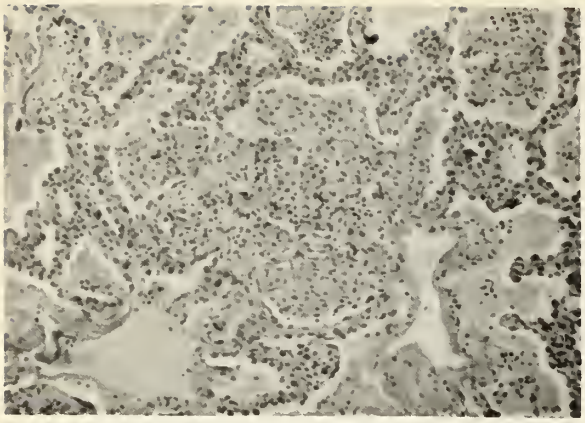

Figure 7.—Open lung biopsy specimen from a patient with pneumocystosis. Hematoxylin and eosin stain, ×400.

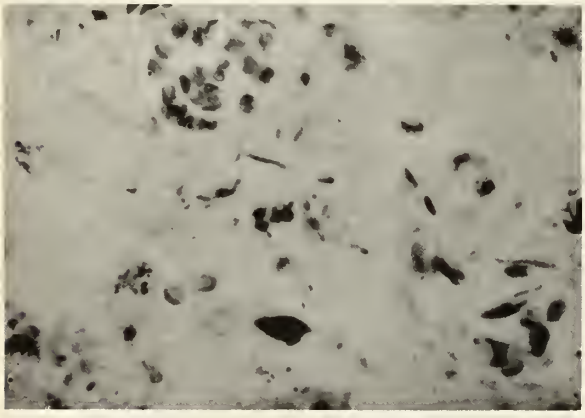

Figure 8.—Open lung biopsy specimen from a patient with pneumocystosis. Methenamine silver stain, ×800.

monary disease, that require histopathologic examination for specific diagnosis. Because effective therapy is available for some of the latter conditions, invasive diagnostic techniques are warranted in immunocompromised patients with undiagnosed pulmonary infiltrates. This is certainly true if needle aspiration is unrewarding or the infiltrate is progressing despite antimicrobial therapy.

With hematoxylin and eosin stains, the most prominent feature of early P. carinii pneumonitis is an eosinophilic foamy exudate filling the alveolar spaces, associated with a scanty mononuclear interstitial infiltrate.[69,105] This appearance is virtually pathognomonic of P. carinii pneumonitis. As the disease progresses, the interstitial infiltrate becomes dense and some fibrosis occurs (Figure 7). Silver stains show the alveoli filled with trophozoites (Figure 8). Touch preparations of lung biopsy material may show the cysts even more dramatically (Figure 9).

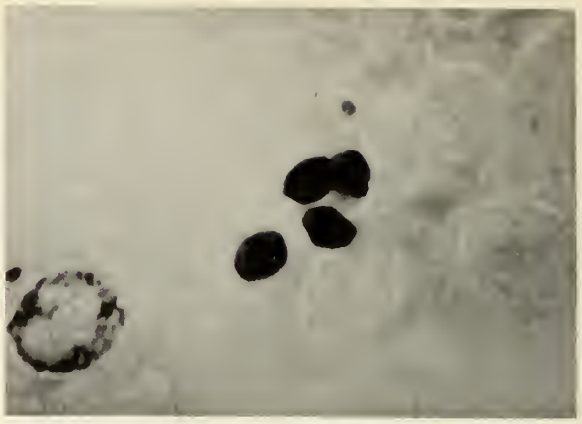

Figure 9.—Tissue touch preparation of open lung biopsy specimen from a patient with pneumocystosis. Methenamine silver stain, ×1,200.

TABLE 8.—*Pneumocystis carinii Antigenemia Detected by Counterimmunoelectrophoresis**

Patient Group	*Number of Patients*	*Percent with Antigenemia by CIE*
Documented pneumocystosis ...	123	68-95
Cancer, without pneumonia	100	15
Normal children	120	0

CIE = counterimmunoelectrophoresis

*Adapted from Pifer et al.[68]

There is some hope that serologic procedures will aid in the diagnosis of Pneumocystis infection. A complement fixation test for Pneumocystis antibody has been used in Europe for many years, particularly in infants and children. Because pneumocystosis tends to be more subacute in onset in these patients than in adult immunocompromised hosts, the test appears to be relatively effective and a detection rate of better than 75 percent has been reported.[57] Use of the complement fixation test in immunosuppressed adults has not been helpful.[76,79] A recently developed immunofluorescent antibody assay was tested by investigators at the Center for Disease Control in Atlanta, Georgia, and was positive in fewer than 1 percent of normal subjects and in fewer than 4 percent of contacts of patients with clinically apparent pneumocystosis; however, only 28 percent of immunosuppressed patients with documented P. carinii infection had antibodies.[75,76] Thus, the test is specific but relatively insensitive. A counterimmunoelectrophoretic assay for P. carinii antigen recently was developed by Pifer and associates,[77] and it appears considerably more promising for the diagnosis of acute disease (Table 8). In a series of 123 cancer patients with

documented pneumocystosis, 68 percent to 95 percent had antigenemia. When fresh sera from 20 patients with documented pneumocystosis were tested with this assay, 19 were positive ($P < 0.05$). Of patients with cancer without pneumonitis, 15 percent were also positive, suggesting possible subclinical infection or reactivation. None of 120 normal children tested had detectable antigen. This test requires further evaluation but appears promising.

Treatment and Prophylaxis

Only a limited number of drugs are available for treatment of P. carinii infection. Pentamidine isethionate (Lomidine) and hydroxystilbamidine are effective in animals and until recently pentamidine was the standard drug used in humans.[88] Although effective in 50 percent to 70 percent of patients, it is quite toxic; and in the United States it is classified as an experimental drug available only through the Center for Disease Control. Recently, a controlled trial was conducted by Hughes and co-workers that compared trimethoprim-sulfamethoxazole (TMP-SMX) (Bactrim, Septra) with pentamidine in the treatment of P. carinii pneumonitis in children with acute lymphatic leukemia.[106] A preliminary study of TMP-SMX in cortisone-treated rats had shown that it was as effective as pentamidine in the treatment of P. carinii pneumonitis.[107] The success rates were comparable in the two patient treatment groups (77 percent compared with 75 percent), but the incidence of toxicity was significantly higher in the pentamidine-treated patients.[106] The dosage used was 20 mg of TMP and 100 mg of SMX per kilogram of body weight per day in four equal doses given by mouth. A parenteral preparation of TMP-SMX is under investigation, and this would facilitate therapy in extremely ill patients. Although the related drug combination of pyrimethamine-sulfadiazine is effective in patients with toxoplasmosis and has been shown to be curative in animal models of P. carinii pneumonitis, it has not received adequate clinical trials to allow determination of efficacy in patients.[108]

Based again on data from the rat model of P. carinii pneumonitis,[107] Hughes and his collaborators at St. Jude's Childrens Hospital in Memphis, Tennessee, undertook a controlled trial of TMP-SMX prophylaxis in children with acute lymphatic leukemia.[109] Pneumocystis pneumonitis did not develop in any of the 80 children treated prophylactically with TMP-SMX (5 mg of TMP and 20 mg of SMX per kilogram of body weight per day), whereas the illness occurred in 21 percent of the 81 children who received a placebo.[109] Consequently, all children with acute lymphatic leukemia at St. Jude's Childrens Hospital who are at high risk for pneumocystosis have received prophylactic treatment with TMP-SMX. Pneumocystis pneumonitis has virtually disappeared from this institution, despite an increase in the number of patients being treated for acute lymphatic leukemia (Figure 10). At present, TMP-SMX is the treatment of choice for P. carinii pneumonitis, and it should be used prophylactically in certain high-risk patients in whom the develop-

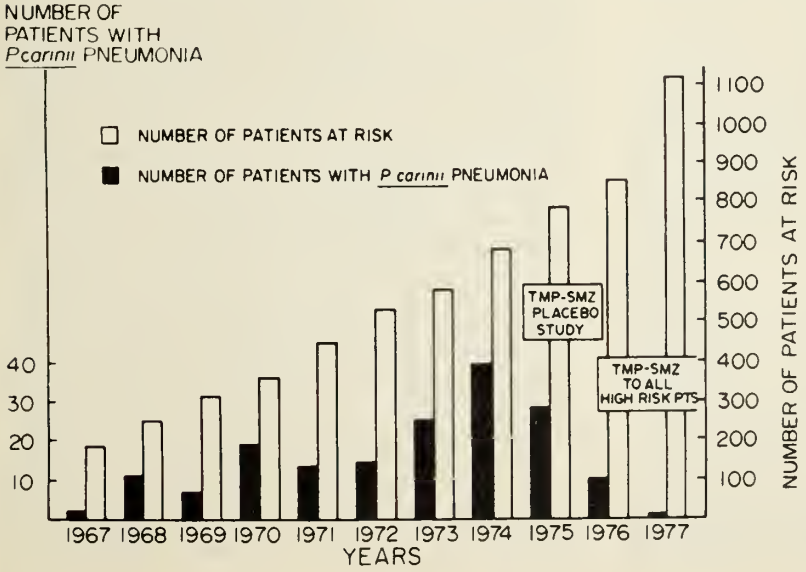

Figure 10.—Effect of trimethoprim-sulphamethoxazole (TMP-SMX) prophylaxis on the incidence of P. carinii pneumonia at St. Jude's Childrens Hospital, Memphis, Tennessee, 1967-1977. From October 1974 to October 1976, high-risk patients were randomly assigned to receive TMP-SMX or placebo; thereafter, all high-risk patients received TMP-SMX chemoprophylaxis. (Reprinted by permission from Hughes WT, Kuhn S, Chaudhary S, et al, and the *New England Journal of Medicine:* N Engl J Med 297:1419-1426, Dec 1977.[109])

ment of this condition is likely. Because instances of possible resistance of P. carinii to pentamidine have been reported, TMP-SMX prophylaxis should not be used indiscriminately.[69,88]

In summary, substantial advances have been made recently in our knowledge of P. carinii pneumonitis. The organism has been grown *in vitro,* and a possible role for antibody as an opsonin has been demonstrated in cell culture. Serologic studies have shown that the infection is prevalent in humans, suggesting reactivation as the major mechanism of clinical disease. Animal-to-animal aerosol transmission has been documented. Clinically, the relatively nontoxic drug TMP-SMX has been shown to be effective for both treatment and prophylaxis. A counterimmunoelectrophoretic assay for Pneumocystis antigen shows promise of being useful diagnostically. Sophisticated respiratory support has allowed survival of patients with respiratory failure through the period of antiparasitic drug therapy. However, there is still much need for investigation. The taxonomic position of the organism has not been determined precisely, and the antigenic and biologic relationships between animal and human strains have not been evaluated fully. The definitive reservoir (for human infection) has not been identified, and the spectrum of subclinical infection or disease has not been defined in either the normal or immunosuppressed host. Human disease is assumed to be due to reactivation of latent infection, but proof is lacking. Most important, we have no knowledge of how the organism produces disease, and the host defense mechanisms effective again P. carinii pneumonitis have not been defined.

Conclusion

From this discussion, it should be apparent that Pneumocystis and Toxoplasma share certain characteristics (Table 9). They are both found in man and in a wide variety of animals, usually in a latent form, emerging as opportunistic pathogens when host defenses are impaired. Toxoplasma is the more efficient pathogen of the two because it can cause disease in the normal host unlike Pneumocystis, which rarely, if ever, produces clinically apparent infection in a host with intact defense mechanisms. A large segment of the population has antibodies to Toxoplasma and Pneumocystis, reflecting widespread exposure. Both organisms are found in tissue as cysts and trophozoites. In the compromised host, both parasites exhibit

TABLE 9.—*Similarities Between Toxoplasma and Pneumocystis*

Factor	*Toxoplasma*	*Pneumocystis*
Host	Animal/human	Animal/human
Laboratory propagation		
Artificial media	−	−
Tissue culture	+	+
Laboratory animals	+	+
Infection normal host	Most asymptomatic	Most asymptomatic
Latency	+	+
Opportunistic pathogens	+	+
Intracellular parasitism	+	−
Tissue tropism	Brain	Lung
Treatment available	+	+
Concomitant infection by cytomegalovirus	+	+

tissue tropism, with Pneumocystis representing the purer example of organ predilection because it is rarely found in extrapulmonary sites. Toxoplasma has a predilection for the central nervous system, but it can affect virtually any organ. Neither organism can be cultivated on artificial media; they both require cell culture or laboratory animals for propagation. Toxoplasma is an obligate intracellular parasite, whereas the available evidence suggests that Pneumocystis exists primarily extracellularly. Effective therapy is available for both parasites, and it is remarkable that both drug combinations employed to treat infections with these organisms interfere with folic acid metabolism. Finally, both organisms are associated with concomitant cytomegalovirus infection in the setting of immunosuppression at a frequency that would suggest more than a chance relationship.

In closing, let us consider some possible explanations for concomitant infections of Toxoplasma and Pneumocystis with cytomegalovirus. In experimental animals, infections with either cytomegalovirus or Toxoplasma can suppress cell-mediated immunity.[110,111] This segment of the immune system appears to be critical in the defense of the host against Toxoplasma[30] and cytomegalovirus[112] and likely is important in the control of Pneumocystis infection. Thus, the immunologic insult of a single infection, compounding others produced by treatment or malignancy, may well promote secondary infection. Another hypothetic explanation for concomitant parasite-virus infections might be an interaction of these organisms that would facilitate colonization of the potential host. For example, these two parasites might serve as a vector for cytomegalovirus. In fact, in a recent electron microscopic study of P.

carinii, structures were found within the cytoplasm of this parasite that resemble cytomegalovirus.[113] Finally, there may be some symbiotic relationship between these organisms in which elements essential to growth of one organism are provided by the other organism. Such a relationship has been suggested for Toxoplasma and cytomegalovirus because of the frequent finding in autopsy series of cells infected with both agents.[10] Lending support to this suggestion is a unique intracellular anatomic relationship of the two organisms that consists of Toxoplasma trophozoites surrounding inclusion bodies containing mature virus. One would not expect this relationship if dual infection of these cells was nothing more than a random event.

In summary, Toxoplasma and Pneumocystis are important opportunistic pathogens that account for significant morbidity and mortality in the compromised host. There is obviously a need to understand the pathogenic mechanisms responsible for disease production by these organisms. The occurrence of concomitant infection of these parasites with cytomegalovirus suggests more than a fortuitous relationship. If one could demonstrate a symbiotic relationship or an additive or synergistic suppressive effect of dual infection on the immune system, therapy directed at controlling one of these organisms might reduce the pathogenic potential of the other organism. Thus, an understanding of these relationships is more than of academic interest because it may suggest a means of controlling these important pathogens.

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Specialty Conference

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Intussusception

MARTIN STEIN, MD:* Pediatricians are confronted frequently with infants and toddlers who present with the acute onset of vomiting and abdominal pain. Experienced clinicians are aware that, while gastroenteritis, acute appendicitis, respiratory inflammatory processes, poisoning and urinary tract infections most often account for these symptoms, various forms of intestinal obstruction, though uncommon in young children, must be diagnosed immediately. In particular, intussusception has a reputation for its protean presentation and all-too-frequent delay in diagnosis.

Intussusception is defined as the invagination of one portion of the intestine into another in the direction of peristalsis. The Latin *intus* means "within" and *suscipere* means "to take up." The most common type is ileocolic; less common forms include ileal-ileal, colic-colic and ileal-ileal-colic. The development of intussusception in children is characteristically a spontaneous event during infancy and occurs in previously healthy, well-nourished patients. Two thirds of patients are between 3 and 12 months of age. Less commonly, it may occur in older children, either spontaneously or in association with a leading point—that is, an anatomic lesion that initiates the intestinal invagination process. Known leading points include enlarged mesenteric nodes, hypertrophied Peyer† patches in the distal ileum, Meckel diverticulum, polyp, enteric cyst, intramural hematoma, ileal duplication, lymphosarcoma, inspissated meconium associated with cystic fibrosis and Henoch-Schönlein purpura. Fewer than 10 percent of children with intussusception have a leading point; its occurrence is even less common, perhaps 2 percent to 3 percent, in children less than 2 years old.

The development of intussusception is associated with venous stasis in the mesenteric vessels, followed by engorgement and edema of the bowel wall that progresses to strangulation. The compromise of the vasculature, which results from the intussusception, produces colicky pain, reflex vomiting and bloody stools. The so-called currant-jelly stool is pathognomonic of intussusception. At times, a mass may be palpated at some point along the course of the colon; this mass represents the intussusception, bowel inside bowel, with its consequent edema and trailing mesentery and vessels. An astute clinician may detect an emptiness in the right lower quadrant that reflects the movement of

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†The WESTERN JOURNAL'S style regarding eponyms is that they are not written in the possessive form; therefore, Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

the distal ileum and cecum away from their usual position. Eventually, if this process is allowed to continue, intestinal obstruction will ensue. If gangrene sets in, perforation and peritonitis will develop.

The goal of the primary pediatrician is to diagnose intussusception at an early stage in the disease process when reduction by barium enema may be possible, thereby permitting the avoidance of operative intervention. Several recent cases provide the framework for discussion in this Specialty Conference.

ANDRE RASZYNSKI, MD:* CASE 1. A 5-month-old girl was brought to her pediatrician with a history of occasional vomiting and diarrhea and episodes of crying and irritability over a 24-hour period. She had been in excellent health before this episode. On physical examination the infant was noted to be afebrile, well-hydrated and relaxed. The abdomen was soft and nontender. A diagnosis of acute gastroenteritis was made, and the parents were advised to provide a clear liquid diet and to make a follow-up phone call. As the infant and parents were leaving the pediatrician's office, the patient developed a sharp cry and opisthotonic posturing. Immediate examination included a rectal examination which yielded an explosive currant-jelly stool. When the baby quieted, the abdomen was again soft and without palpable mass.

At this time, the pediatrician suspected intussusception. A plain roentgenogram of the abdomen showed a density in the area of the transverse colon. A barium enema documented an intussusception in the distal transverse colon. Complete reduction of the intussusception was accomplished by means of hydrostatic pressure with barium. The barium was followed through the colon and into the small bowel. A follow-up scout film six hours postreduction did not show any evidence of obstruction or recurrence.

DR. STEIN: The acute onset of vomiting, colicky abdominal pain and rectal bleeding in a previously healthy infant represents the cardinal symptomatology of intussusception. Although all three symptoms were eventually evident in this patient, it was logical that the physician initially made a diagnosis of gastroenteritis. It is not typical, but the patient with acute intussusception may appear very well between episodes of colic. More often the infant is listless and apathetic. Episodes of pain usually recur at 10- to 30-minute intervals. Fortunately, this patient's colic, severe enough to induce posturing, recurred before departure from the physician's office, and a second examination was carried out. The importance of the rectal examination, which may yield a bloody stool, is pointed up by this case. In most children with intussusception, an abdominal mass may be palpated, but it may not. The absence of a palpable mass may delay the diagnosis unless the clinician is suspicious of intussusception.

CASE 2. A 15-month-old boy presented to the hospital after a 24-hour history of vomiting, anorexia and intermittent abdominal pain. There had been no respiratory symptoms, fever, trauma or unusual ingestion. He had been in excellent health before this illness. On physical examination he was noted to be comfortable but quiet between episodes of abdominal pain that occurred every three minutes. During these episodes he would flex his hips, moving his thighs to his abdomen, and cry in pain. The temperature was 36.6°C (98°F). There was a mobile nontender right periumbilical mass that measured 2 cm by 5 cm. Rectal examination yielded bloody, mucoid stool. A plain film of the abdomen showed, in the middle of the lower abdomen, a single dilated loop of small bowel without an air-fluid level. There was a suggestion of a mass in the right upper quadrant.

The history and physical and roentgenographic findings suggested intussusception, and a barium enema showed an intussusception in the midportion of the transverse colon. Attempted reduction by hydrostatic pressure moved the mass only to the ascending colon. The child was taken immediately to surgery, and an ileocecal intussusception was found in which approximately 5 cm of ileum extended the length of the ascending colon to the hepatic flexure. Reduction was accomplished without difficulty by means of gentle pressure. The surgeon noted several large (3 cm by 5 cm) mesenteric nodes. An appendectomy was done. The child did well postoperatively.

This case was typical of childhood intussusception in that (1) it occurred in a previously healthy infant (approximately 75 percent of cases are in children less than 2 years old); (2) the patient was a boy (it affects males more frequently than females by a ratio of 3:2); (3) vomiting and colicky abdominal pain were the presenting symptoms; (4) a mass was palpated in the right upper quadrant (abdominal masses have been discovered

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by palpation in some 20 percent to 90 percent of patients in reported cases[1,2]).

Reduction by barium enema was not successful. In general, when symptoms last longer than 24 hours the chance for complete reduction by enema is decreased. However, in most patients with intussusception, barium enema reduction, with a maximum of 3 feet of hydrostatic pressure, should be attempted. With this pressure limit, Ravitch has pointed out that gangrenous bowel will not reduce and perforation will not occur.[1]

At surgical operation large mesenteric nodes were observed. Although mesenteric adenitis may be secondary to a viral infection, attempts to document acute viral illness, especially advenovirus infection, in patients with mesenteric adenitis and intussusception have been equivocal.

WILLIAM NYHAN, MD, PHD:* It is of interest to remember that after 24 hours of symptoms, this child did not produce a bloody stool. It was only in association with the rectal examination that a bloody, mucoid stool was identified. Bloody stools are more common in children less than 2 years old than they are in older children with intussusception, but of course this child was less than 2. Following the rectal examination, he passed a bright red stool with mucus. This is worth emphasis because in my view this is the classic currant-jelly stool. In these patients enormous amounts of mucus are produced. They may pass pure mucus per rectum and I have even seen patients with intussusception produce mucus in vomitus and by stomach tube. The so-called currant-jelly stool is an admixture of blood and mucus, and usually it is an imperfect streaky mixture, which no one would really mistake for jelly.

DR. STEIN: CASE 3. An 8-month-old boy was in excellent general health until the morning of admission. Upon awakening, he had a dark brown, diarrheal stool and started crying intermittently. He drank 8 oz of milk but then began vomiting. His pediatrician father stated that it appeared his son was experiencing abdominal pain. He became progressively more lethargic and appeared gravely ill. On physical examination he was afebrile. He appeared seriously ill and was described as septic in appearance. He had alternating periods of lethargy and crying every three to five minutes. When crying, he would flex his hips and knees, flail his arms and arch his back. The blood pressure was 100/60 mm of mercury. His neck was supple. There were no local areas of infection. Initial abdominal examination showed no abnormalities. The admitting diagnosis was sepsis. A lumbar puncture was normal. The leukocyte count was 17,600 per cu mm, with a left shift. Analysis of urine produced normal findings. Rectal examination yielded a minimal amount of guaiac-positive stool.

A subsequent examiner noted a firm, discrete, tubular mass in the right upper quadrant in an otherwise soft, nontender abdomen. A barium enema showed at the midtransverse colon a coiled spring appearance that was consistent with intussusception. Partial reduction by hydrostatic pressure moved the mass to the cecum. At surgical operation an ileoileal-colic intussusception was found at the midpoint of the ascending colon. It was reduced by gentle digital pressure. An appendectomy was done, and the child had an uneventful postoperative course.

This infant's course is an example of the profound lethargy and prostration that may be associated with intussusception at an early stage in the disease process. His initial appearance suggested shock, sepsis or meningitis. A normal blood pressure and normal findings on prompt examination of the cerebrospinal fluid suggested an alternative diagnosis.

It is characteristic of intussusception, especially in infants, to find a flaccid, exhausted patient between the attacks of abdominal colic. The abdomen is typically not distended, and tenderness may be absent or localized to the mass. A diagnosis of intussusception may be delayed until an abdominal mass is palpated. When the third examiner located a right upper quadrant mass in this patient, a barium enema was performed in order to substantiate the diagnosis. A high index of suspicion of intussusception in a young patient with vomiting and intermittent abdominal pain, coupled with careful examinations of the abdomen, will clarify the diagnosis. Occult blood in the stools or grossly bloody stools are helpful observations.

In young children, a barium enema will completely reduce the intussusception in approximately 75 percent of patients. A short duration of symptoms is said to be associated with a high reduction rate by barium enema. In this patient, an ileoileal leading point was found invaginating into the ascending colon, as opposed to the more typical ileocolic form of intussusception. Perhaps

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this anatomic variant prevented complete reduction by barium enema.

This patient did not have currant-jelly stools. He had only brown diarrheal stool that contained occult blood. The finding of normal stool on rectal examination, free of gross or occult blood, argues against the diagnosis of intussusception in patients in whom symptoms have been present a few hours.[3]

CASE 4. A 9-month-old boy was in good health until two days before admission when a mild cough, vomiting, constipation and intermittent episodes of a high-pitched cry associated with arching of his back, developed. He was admitted to a local hospital with an admitting diagnosis of an acute neurologic disease—meningitis, encephalitis or subdural hematoma. Lumbar puncture showed clear acellular cerebrospinal fluid, with normal concentrations of protein and glucose. A nurse reported brief episodes of lapsing into coma, followed by high-pitched crying with arching of the back. The infant was transferred to University Hospital, where episodes of screaming and arching of the back were observed. Physical examination showed a temperature of 37°C (98.6°F) and abdominal fullness in the right upper quadrant, with mild tenderness and guarding. There was no clearly definable mass. Although the child had not passed a stool in two days, rectal examination was followed by a currant-jelly stool.

A plain roentgenogram of the abdomen showed multiple dilated loops of small bowel without dilatation of the colon, consistent with small-bowel obstruction. A barium enema defined an intussusception of the midtransverse colon, which was reduced only partially to the cecum after two attempts with hydrostatic pressure.

At surgical operation, the distal 15 cm of the terminal ileum was found to have invaginated up the ascending colon to the hepatic flexure. Following surgical reduction, a firm, spherical 2-cm mass on the antimesenteric wall of the ileum was seen to act as a leading point. The mass was removed by wedge resection. Pathological examination showed a fluid-filled cystic structure lined by simple columnar epithelium. The histology was that of an enterogenous cyst, an inclusion cyst of the small bowel. The patient did well postoperatively.

This infant's disease was unusual in that an anatomical leading point was the cause for the intussusception. In children less than 2 years old, fewer than 3 percent of the patients have leading points. Meckel diverticulum is the most common of these.

The presenting findings in this patient suggested an acute neurological disorder rather than an abdominal emergency. Later in the course, fullness in the right upper quadrant, as opposed to a discrete mass, was found. The plain film of the abdomen was helpful in suggesting an obstructive process.

CASE 5. The patient, a 6-year-old boy, was in excellent health when he awoke at 2 A.M. complaining of severe periumbilical pain. The pain was characterized as intermittent. Every two to three minutes he would double over with pain, which migrated to the lower abdomen over the next few hours. The pain lasted approximately a minute. At home, he passed a large, bright red, bloody stool shortly after the onset of pain. He vomited several times.

On physical examination, six hours after the onset of pain, the child was noted to be afebrile and normotensive. His abdomen was diffusely tender, especially in the lower quadrants. There was no palpable mass. Auscultation showed intermittent rushes and tingling sounds corresponding with the episodes of colic. On rectal examination, a 2-cm mass, extrinsic to the rectum, was palpated at the tip of the examining finger. A guaiac-positive stool was found.

The leukocyte count was 17,500 per cu mm, with a left shift. A plain film of the abdomen showed a small-bowel obstructive pattern. The barium enema defined a multilobulated mass in the cecum consistent with an ileocolic intussusception. Reduction by hydrostatic pressure was unsuccessful.

At surgical operation, an ileocolic intussusception in the cecum was found with a Meckel diverticulum acting as a leading point. Following reduction, the Meckel diverticulum was resected and an appendectomy was done. The patient did well.

This case illustrates the most common source of a leading point, a Meckel diverticulum, associated with intussusception. Although case 4 was an example of an associated leading point in a younger child, this case is more characteristic in that older children are more likely to have a leading point than are patients less than 2 years old.[4]

Although a mass was not found on abdominal examination, the discovery of a mass on rectal examination, along with the history of abdominal colic and vomiting, led to a presumptive diagnosis

of intussusception. Ravitch stated that in 90 percent of patients, an abdominal or rectal mass is palpable. In six of 152 patients, the mass was palpated on rectal examination but not on abdominal examination. In 11 of 152 patients, the mass made a dramatic presentation through the rectum.[5]

PHYSICIAN IN AUDIENCE: *If you were successful at reducing this child's intussusception by barium enema, you may have missed the opportunity of discovering the Meckel diverticulum and thereby increased the child's risk for a recurrence.*

DR. STEIN: You are correct in pointing out one pitfall of barium enema reduction. Since children more than six years old who have intussusception are at much higher risk for an associated leading point, some pediatric surgeons plan elective exploratory laparotomy following successful barium enema reduction in older patients. Most pediatric patients with intussusception are children less than 2 years of age, who are much less likely to have an associated leading point. Alternatively, you might look for a leading Meckel diverticulum, using a sodium pertechnetate Tc 99m scan,[6] following successful nonoperative reduction in older patients. However, this approach would bypass the occasional older child whose intussusception is the first clinical manifestation of an intestinal lymphosarcoma; this is important because an isolated intestinal lymphosarcoma is curable by surgical operation. Actually, this is not a significant practical problem because most intussusceptions with leading points are not reducible by barium enema.[4]

RICHARD BUCHTA, MD:* CASE 6. I recently saw an adolescent patient with an atypical form of intussusception. Because of his age, a lymphosarcoma was considered preoperatively. He was a 14-year-old boy who was admitted for evaluation of intermittent acute abdominal pain of ten days' duration. He had had an appendectomy at the age of 3 years. His father was listed as MIA (missing in action) in the Vietnam war, and the boy had been under psychiatric care from the age of 7 until he was 10 years old.

Acute abdominal pain had developed in this patient, associated with one episode of emesis three days after the government announced that no MIA's were considered to be still alive. Examination at that time showed no abnormalities. A clear liquid diet was prescribed, and the pain subsided. Three days later there was recurrence of severe cramping pain in the lower abdomen. No fever, emesis, hematochezia or diarrhea was present. Examination showed tenderness over the region of the appendiceal scar. Rebound tenderness was questionable. Results of complete blood count, determination of erythrocyte sedimentation rate and analysis of urine were normal. Pain subsided over the next few hours, and again the boy was asymptomatic for three days. Pain recurred, and a barium enema study was done. The films showed a large filling defect in the cecum with a coiled-spring appearance typical of intussusception. It could be only partially reduced; and, under fluoroscopy, there appeared to be, in the area of the appendiceal stump, a mass acting as a leading point for a colocolonic intussusception.

Figure 1.—Roentgenogram indicates a mass on the right side of the abdomen.

Because of the possibility of malignant tumor, a three-day bowel preparation was administered, and a right hemicolectomy was done. Pathological examination showed a 4-cm mass that almost filled the cecum. This mass consisted of a fecalith in a cavity communicating with the lumen of the cecum by means of a 1-cm opening and containing a 0.5-cm lumen. The cavity was lined by intestinal mucosa. It is postulated that this cavity was related to the earlier appendectomy. The lumen was in the area and about the same size as the normal orifice of the appendix. This must have developed suffi-

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Figure 2.—The barium enema study shows an obstruction in the midtransverse colon.

Figure 3.—The intussusception was reduced successfully by hydrostatic pressure.

cient patency to allow fecal material to enter and become trapped in the cavity, giving rise to the fecalith. A large fecalith in an intramural cyst leading to intussusception has not previously been reported.

This adolescent's prolonged course is characteristic of intussusception in older children, in whom an intussusception may remain viable and may be easily reducible as late as four days after the onset of symptoms.[7]

DR. STEIN: We have seen that roentgenograms may show intussusception in several ways. When suspicious of intussusception, a clinician may request an abdominal plain film, which may show a mass, usually on the right side (Figure 1). The mass lesion represents a portion of bowel telescoping inside another portion of bowel. The subsequent barium enema study in this patient showed an obstruction at the midtransverse colon (Figure 2), which was reducible by hydrostatic pressure (Figure 3).

Figure 4.—The plain roentgenogram is nonspecific. There are dilated loops of bowel throughout the abdomen.

When the plain abdominal film reveals a mass or lack of bowel gas in the right lower quadrant, it may aid the clinician. However, the plain film may be normal or nonspecific (Figure 4); a barium enema study in this patient showed there to be a cecal filling defect that was consistent with intussusception (Figure 5). A more characteristic sign of intussusception is the coiled-spring effect that reflects a layering of edematous intussuscepted bowel (Figures 6A and B).

Figure 5.—The barium enema study shows a cecal filling defect which was reduced by hydrostatic pressure.

PHYSICIAN IN THE AUDIENCE: *Following successful treatment, is there a recurrence risk for intussusception?*

DR. STEIN: The recurrence rate has been reported as 2 percent. Apparently the risk of recurrence is similar in those children whose intussusception is reduced by barium enema and in those reduced at surgical operation. However, postoperative adhesions following surgical reduction may lead to obstruction. In children with a recurrence, it is particularly important to consider the possibility of an anatomical leading point. The autosomal dominant Peutz-Jeghers syndrome, in which buccal pigmentation is associated with multiple intestinal polyps, may cause recurrent intussusception with different polyps as leading points. Among the many school-age children who have recurrent abdominal pain without a documented organic cause, repeated episodes of intussusception with spontaneous reduction may be present very rarely. There have been reports of occasional spontaneous reductions that have occurred on the way from the radiology suite to the operating room.

DR. NYHAN: The diagnosis of intussusception can present a real challenge to physicians caring for children. Its manifestations and presentations have been well described as protean. At the same time, the stakes are high, because the prognosis is so very good, provided the diagnosis is made in time

Figure 6.—**A**, The coiled-spring sign of intussusception. **B**, A different but also typical roentgenographic appearance of intussusception.

and appropriate therapy is instituted. Once the disease is suspected, proving the diagnosis is usually easy. Therefore, it is important to us to be aware of the many ways that intussusception can be present.

In this conference, we have discussed two cases in which the presentation was the typical one, with symptoms of vomiting and colicky pain in a previously healthy, usually but not always male infant less than 2 years of age. An ill-defined abdominal mass may be found, with or without bloody or currant-jelly stools. We have also discussed the typical presentation in an older child with a Meckel diverticulum as the leading point. One patient presented with diarrhea, lethargy and an appearance of overwhelming illness. On admission, he was thought most likely to have sepsis. The other infant had intermittent episodes of high-pitched crying and arching of the back and was referred with a diagnosis of acute central nervous system infection. An adolescent patient had an unusual situational presentation against a background of previous treatment for psychiatric disease. Two unusual leading points included a fluid-filled enterogenous cyst and a fecalith in a cystic structure that may have represented an appendiceal stump.

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Hazards of the CVP Catheter in the Heart

BACK IN 1970 I found a series of patients at the University of South Carolina in whom the central venous pressure catheter was placed so that the tip of it lay in the heart. A particular case years ago was a 40-year-old man with multiple trauma . . . and that man died of pericardial tamponade when the catheter tip got trapped up in the auricle, eroded through, and fluids were given into the pericardium. We found three other cases, for a total of four in a short period at our university. This occurrence has been reported since then; it happens all over the country. And I now get at least two calls a year from lawyers concerning testimony in cases in which this has happened to patients. Do not let a central venous line that you have monitoring a patient in shock sit in the heart. In my opinion, it is dangerous.

—CHARLES T. FITTS, MD, *Charleston, South Carolina*
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Refer to: Advances in the understanding of asthma—Medical Staff Conference—University of California, San Francisco. West J Med 130:43-55, Jan 1979

Advances in the Understanding of Asthma

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and Robert C. Siegel, Associate Professor of Medicine and Orthopaedic Surgery, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *In this Medical Staff Conference some of the newer concepts in the pathogenic mechanisms of a common disorder, asthma, will be discussed. Drs. Warren Gold and Jay Nadel of the Cardiovascular Research Institute will lead the discussion.*

DR. GOLD:† The purpose of this review is to analyze current advances in our understanding of asthma. First, we will review the biology of IgE based on studies *in vitro* and then review the roles played by mast cells, chemical mechanisms and nervous mechanisms in IgE-mediated reactions *in vivo*. Next, we will review the concept of airway hyperirritability in asthma and, finally, analyze the mechanisms controlling mucociliary clearance.

Biology of IgE

Figure 1 illustrates the general concept of IgE-mediated allergic asthma developed by immunopharmacologists from studies with isolated tissues.[1] Certain antigens, such as aeropollens, cross the bronchial epithelium and stimulate an immune response in lymphoid tissues. It is uncertain how such large molecules (10,000 to 40,000 daltons) penetrate the bronchial epithelium. One of the basic defects in asthmatic patients may be that their airways are abnormally permeable, permitting inhaled antigens to reach the lymphoid tissue, not only in the periphery, but also in the respiratory tract. The immune system elaborates a specific immunoglobulin (IgE) that has several very important characteristics: (1) IgE is present in minute concentrations in plasma.[2] (2) IgE fixes to tissues (such as mast cells in the lung and the basophils in the circulating blood). On reexposure to the same antigen, two molecules of this specific IgE-antibody react with the antigen. This reaction causes perturbation of the membrane of

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The studies by Dr. Gold on the biology of IgE were performed with D. Y. C. Yu, G.-F. Kessler, and O. L. Frick; on mast cells with G. L. Meyers, D. S. Dain, R. L. Miller, and H. R. Bourne; on 48/80 with M. R. Nisam, A. Zbinden, S. Chesrown, and D. Barnett; on cyclic nucleotides with D. Barnett, S. E. Chesrown, A. F. Zbinden, M. Nisam, B. Reed, H. R. Bourne, and K. L. Melmon; on tantalum bronchography with G.-F. Kessler, J. H. M. Austin, P. D. Graf, and G. Gamsu; and on vagus nerves with G.-F. Kessler, and D. Y. C. Yu.

The studies by Dr. Nadel on virus infections were carried out with D. M. Empey, L. A. Laitinen, L. Jacobs, L. A. Elkin, and J. Mills; on ozone with L.-Y. Lee and E. Bleecker; on ion transport with M. G. Marin, B. Davis and R. E. Oliver; on mucous gland secretion with B. Davis, M. G. Marin, I. Ueki and P. D. Graf.

ABBREVIATIONS USED IN TEXT

AMP = adenosine monophosphate
ECF-A = eosinophil chemotactic factor of anaphylaxis
GMP = guanine monophosphate
NCF = Neutrophil chemotactic factor of anaphylaxis
PAF = platelet-activating factors
R_{aw} = airway resistance
R_L = resistance to flow
SRS-A = slow reacting substance of anaphylaxis

the target cell to which the IgE molecules are bound and initiates a sequence of biochemical reactions within the cell. This results in the generation of a number of very important chemicals, or mediators of anaphylaxis. At a plasma IgE concentration of only 10 ng per ml (exceeded in 99 percent of healthy and allergic persons), the basophil is functionally saturated and is coated with 4,000 IgE molecules. When this number of IgE molecules is present, exposure of the basophil to anti-IgE causes a maximal release of mediator from the cell. Basophils from healthy subjects will release less than 25 percent of their stored mediators; basophils from allergic subjects will release more than 85 percent of their mediator content. Therefore, another important feature of the allergic state is the abnormal release of mediators.

Chemical Mediators of Anaphylaxis

Three types of mediators are illustrated in Figure 1.[1] Histamine is released in all mammalian species when IgE reactions are triggered.[2] Histamine causes smooth muscle contraction and increased permeability of the venous end of the capillary.

Slow reacting substance of anaphylaxis (SRS-A) is poorly defined chemically. It is an acidophilic lipid, not a peptide or prostaglandin, with a molecular weight of 400 daltons. There are some studies *in vitro* and *in vivo* suggesting that SRS-A produces sustained contraction of airway smooth muscle in guinea pigs and some monkeys, but not in dogs. More recently, Wanner and co-workers suggested that SRS-A inhibits mucociliary transport.

Eosinophil chemotactic factor of anaphylaxis (ECF-A) is one of a number of chemotactic factors released by the antigen-antibody interaction which attracts different cell types to the site of the immune response. ECF-A attracts eosinophils containing chemicals that inhibit IgE reactions: aryl-

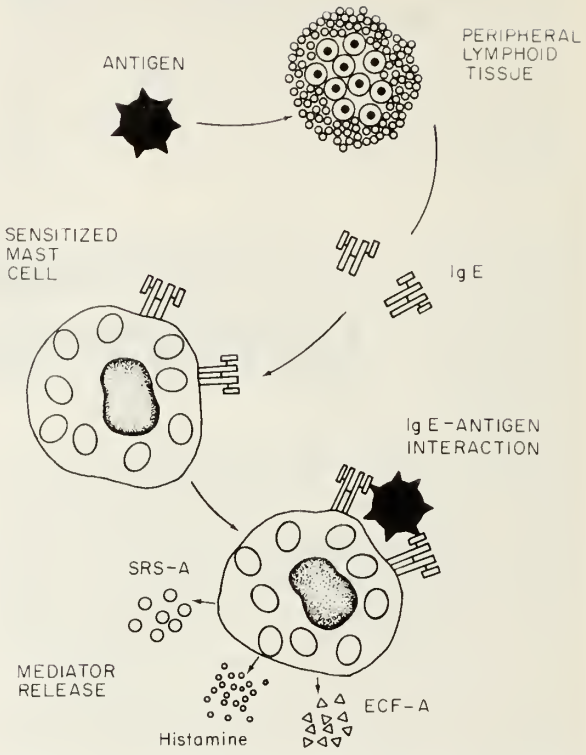

Figure 1.—Molecular mechanisms of mediator release in asthma. Antigen exposure stimulates peripheral lymphoid tissues in atopic persons to synthesize IgE. The IgE antibody becomes fixed by its Fc portion to certain cells (such as circulating basophils in the blood or mast cells in the tissues). On repeated exposure, the same antigen reacts with the antigen receptors on the Fab portion of two IgE molecules. The IgE-antigen interaction activates enzyme systems within the cell which cause the release of mediators of anaphylaxis. In lung tissue at least three mediators may be released, including histamine (bronchospasm), slow reacting substance of anaphylaxis (SRS-A, prolonged bronchospasm), and eosinophil chemotactic factor of anaphylaxis (ECF-A, eosinophil exudate). (Reproduced from Gold[1] with permission from Academic Press, Inc.)

sulfatase B inactivates SRS-A, histaminase inactivates histamine and phosphorylase D degrades certain platelet-activating factors. The action of these compounds will tend to localize or limit the severity of the reaction. Other chemotactic factors such as neutrophil chemotactic factor of anaphylaxis (NCF) attract neutrophils which may release lysosomal enzymes causing pronounced inflammation and augmentation of the reaction.[3] Finally, there are platelet-activating factors (PAF) released from the target cells which can liberate potent chemicals, such as serotonin, from platelets which may not only affect airway smooth muscle directly, but also augment the response to vagally mediated reflexes.

Modulation by Cyclic Nucleotides

Other studies *in vitro* suggest that the IgE-mediated antigen-antibody reaction is modulated by the second messengers, cyclic adenosine monophosphate (AMP) and cyclic guanine monophosphate (GMP). Figure 2 shows the effect of increasing levels of cyclic AMP by beta-adrenergic stimuli, whether by synthetic drugs administered for treatment (such as isoproterenol), or by circulating epinephrine, or the release of norepinephrine from adrenergic nerves. Each of these compounds appears to act on the beta receptor activating adenyl cyclase which synthesizes cyclic AMP. This, in turn, results in inhibition of the release of mediators by IgE.[2]

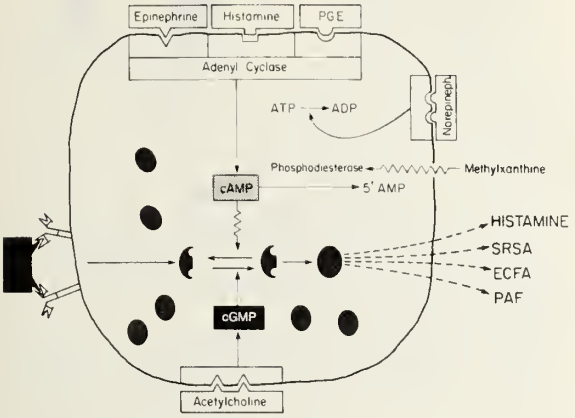

Figure 2.—Effects of endogenous hormones and mediators of inflammation on mast cells. Antigen reacts with two molecules of IgE-antibody fixed to the sensitized mast cell **(left).** This triggers an enzyme-dependent series of biochemical reactions leading to the release of mediators from the mast cell granules. These mediators may include histamine (smooth muscle contraction, increased capillary permeability), SRS-A: slow reactive substance of anaphylaxis (smooth muscle contraction and perhaps impaired mucociliary clearance), ECF-A: eosinophil chemotactic factor of anaphylaxis (attracts eosinophils to reaction site), and PAF: platelet activating factor (activates platelets leading to release of serotonin). Mediator release is augmented by increased levels of cyclic guanine monophosphate (cGMP). Increased cGMP results from stimulation by cholinergic agents administered exogenously or perhaps released during a vagal reflex response. Mediator release is inhibited by increased levels of cyclic adenosine monophosphate (cAMP). Increased cAMP results from adenyl cyclase-mediated synthesis from adenosine triphosphate (ATP). Adenyl cyclase is stimulated by endogenous hormones such as epinephrine and by mediators of inflammation such as histamine or prostaglandin (PGE). Each agent appears to have its own specific receptor site. Increased cAMP may also result from decreased catabolism if degradation by phosphodiesterase is inhibited (for example, by exogenous methylxanthine). Some work suggests that decreased cAMP may result from actions of norepinephrine (activates ATPase), resulting in augmentation of mediator release.

Thus, the release of mediators by antigen is modulated by intracellular levels of cyclic nucleotides. The complex control system permits local negative feedback terminating the reaction and localizing the response (for example, histamine or PGE effect). It also permits positive feedback to occur augmenting the reaction and leading to a generalized inflammatory response (for example, acetylcholine, norepinephrine).

Figure 2 also illustrates the action of another cyclic nucleotide, cyclic GMP. This cyclic nucleotide is increased by cholinergic stimuli and appears to augment IgE-induced release of chemical mediators. Therefore, there appears to be a "push-pull" mechanism to modulate the reactions produced by the physicochemical interaction between antigen and antibody. Kaliner and associates[4] have shown that antigen-induced release of mediators from passively sensitized human lung is altered by cyclic nucleotides: when synthetic cyclic GMP is administered, there is an increase in the amount of mediator release; conversely, when synthetic cyclic AMP is administered, there is a decrease in the amount of mediator released. Many immunopharmacologists working in this field have assumed that the same thing happens in the smooth muscle itself: that is, increased cyclic AMP is associated with relaxation of the smooth muscle; conversely, increased cyclic GMP is associated with contraction of airway smooth muscle. Although this is an appealing concept with which to analyze the action of antiasthma drugs, more recent evidence suggests that the cyclic nucleotides have much more complex ac-

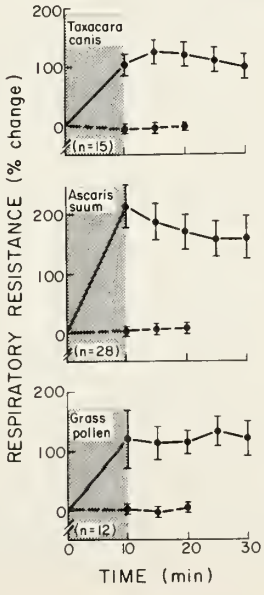

Figure 3.—Effect of different antigen aerosols on respiratory resistance in experimental canine asthma. Solid line: specific antigen aerosol. Dashed line: control aerosol containing extract to which the dog had a negative skin test. Each point represents the mean percent change in resistance ± SE. The shaded zone indicates the period of aerosol inhalation. n = number of dogs studied. (Reproduced from Gold with permission from Academic Press, Inc., Ref. 1.)

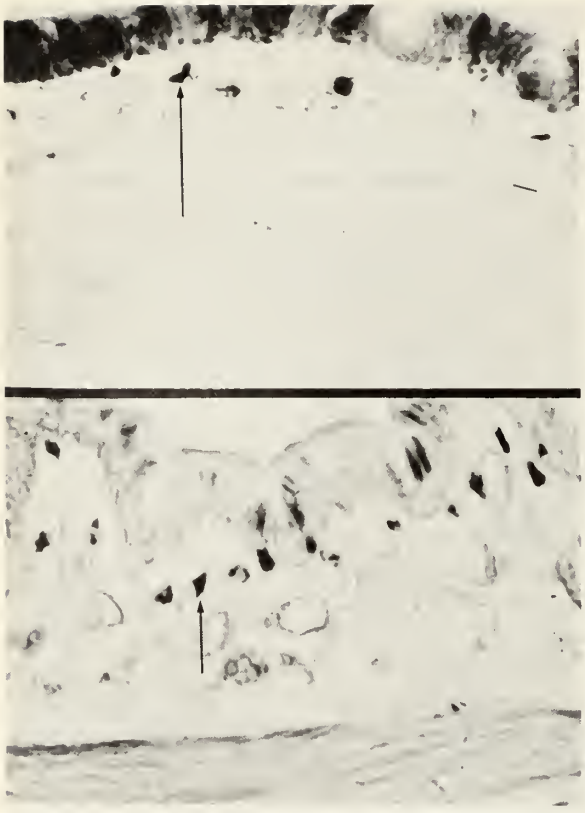

Figure 4—Mast cells in airways of natively allergic dogs. Photomicrographs of a 5-mm bronchus **(bottom)** and a 1-mm bronchus **(top)** from the lung of an allergic dog. The slide has been stained with toluidine blue which stains the granules in the mast cells (indicated by the arrows).

tions in smooth muscle and that both nucleotides may actually inhibit smooth muscle tone.

Experimental Canine Asthma

There are a number of problems in studying IgE-mediated reactions in isolated cell systems, lung fragments and lung slices. The normal anatomic relationships are disrupted, in preparing the tissues receptors may be exposed which are not normally accessible *in vivo,* and the normal neurohumoral control mechanisms cannot be studied in isolated systems. For these reasons, we have developed a preparation *in vivo* using natively allergic dogs. We chose dogs because they are the only animals that develop a naturally occurring respiratory pollenosis similar to humans. This respiratory reaction appears to be mediated by an immunoglobulin that is similar physically, chemically and biologically to human IgE.

Figure 3 shows the increase in airflow resistance caused by three different antigens with which

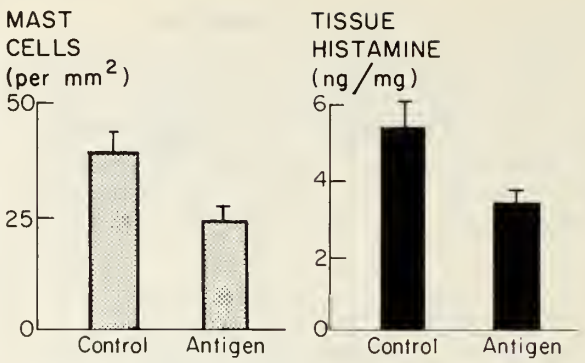

Figure 5.—Effect of antigen on mast cells and histamine in proximal airways. In each of six anesthetized natively allergic dogs, Ascaris suum antigen aerosol decreased the mast cells per sq mm and histamine concentration in the central airways 5 to 7 mm in diameter. No changes in mast cells or tissue histamine concentration were observed in distal airways 1 to 2 mm in diameter. The height of the bar indicates the mean ±1 SE. (Reproduced from Gold, et al[6] with permission from J Appl Physiol.)

we have challenged our dogs. All three antigens increased airflow resistance, which remains increased for about 30 minutes; control antigens, to which the animals had no skin reactivity, produced no airway responses.[5]

Role of Mast Cells in IgE-Mediated Reactions

The target cell of inhaled antigen in the airways of these allergic dogs is the mast cell. Figure 4 shows photomicrographs of a 5-mm bronchus (bottom) and a 1-mm bronchus (top). The slide has been counterstained with toluidine blue which is absorbed by the granules of the mast cells, permitting us to see them. The dark cells below the basement membranes are mast cells; they appear to be waiting for the antigen to cross the mucosa and reach the IgE-antibody presumably fixed to their plasma membranes. There is an inverse correlation between mast cell number (and histamine content) and bronchial diameter. Because of the close correlation between mast cell number and histamine content, we have used the release of histamine as an index of mast cell degranulation.

Physiological Effects of Antigen-Induced Release of Chemicals from Mast Cells

Figure 5 shows the effect of antigen aerosol on large airways of 5 to 7 mm in diameter in allergic dogs. The number of visualized mast cells decreased after antigen because the granules were secreted, dye was no longer taken up by the cells, and therefore the number visualized and counted

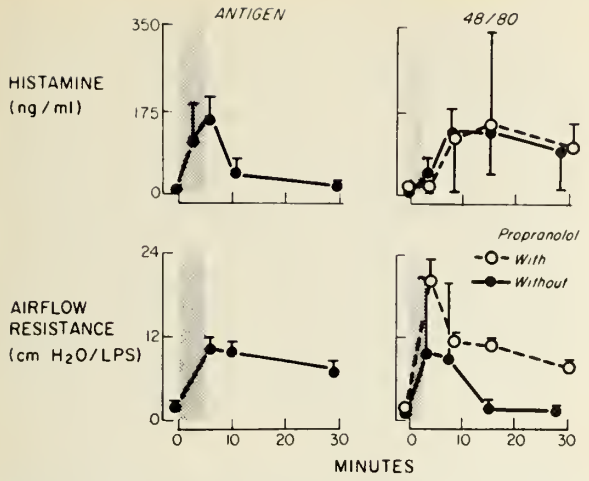

Figure 6.—Effect of antigen aerosol **(left)** and compound 48/80 aerosol **(right)** on release of histamine **(upper)** and airflow resistance **(lower).** Each point is the mean ±1SE (I) of experiments in six dogs with antigen alone (•—•), in eight dogs with 48/80 alone (•—•), and in four dogs with 48/80 during propranolol infusion (o---o). Shaded zone indicates period of aerosol inhalation. (Reproduced from Gold[7] with permission from Am Rev Resp Dis.)

decreased. This figure also shows that there is a parallel decrease in the amount of bronchial tissue histamine after antigen aerosol.[6]

As histamine was released from the tissues following antigen aerosol, it was eluted into the blood perfusing the lung, resulting in a pronounced but transient increase in arterial plasma histamine (Figure 6, left).[7] At the same time, airflow resistance following antigen challenge increased to a maximum corresponding with the release of histamine and then gradually decreased, but not nearly so quickly as the histamine decreased.[8] This suggests that other factors besides the release of stored histamine are responsible for the increased airflow resistance. In an attempt to analyze this process, we have bypassed the immunologic reaction and examined the effect of a pharmacologic agent, compound 48/80, which has been used for many years to degranulate mast cells *in vitro*. It appears to cause secretion of preformed chemicals from the mast cells in a manner similar to antigen. This permitted us to look at a portion of the sequence of reactions induced by antigen.

Physiological Effects of Pharmacological Release of Preformed Chemicals from Mast Cells

Following exposure to compound 48/80 aerosol, there was a decrease in both the mast cell number and the tissue histamine content in the airways, associated with a notable increase in the level of histamine in the plasma leaving the lung (Figure 6, right). The physiologic response to this reaction was characterized by increased airflow resistance and decreased arterial blood pressure.

These animals were treated with chlorpheniramine (which blocks H_1-histamine receptors) and then were challenged with 48/80 aerosol. Although the same amount of histamine was released, the physiologic response of airway smooth muscle was completely inhibited (data not shown). The arterial blood pressure still decreased, but this is not surprising since other workers have shown that the effect of histamine on the blood vessels involves both H_1- and H_2-receptors. These results indicate that secretion of granules from mast cells of allergic dogs results in release of stored mediator, primarily histamine, which acts on the H_1-receptor in the airway smooth muscle.

Cyclic Nucleotide Metabolism in Peripheral Canine Lung in Vivo

Many studies *in vitro* suggest that the initiation and modulation of the reaction induced by antigen-IgE antibody interaction depends on changes in cyclic nucleotide metabolism. Therefore, we have developed a method to evaluate cyclic nucleotide metabolism in our experimental dogs *in vivo* to determine what extrapulmonary and intrapulmonary mechanisms are important in regulating these chemicals. We hope to correlate the changes in cyclic nucleotide levels with changes produced in these animals by pharmacologic agents like 48/80, or by antigen, in order to understand more about the biochemical regulation of the reaction. In anesthetized dogs with open chests, we sampled tissue from within 3 cm of the edge of the lobe with clamps cooled in liquid nitrogen. Under these experimental conditions, the basal level of cyclic AMP was 88 picomoles per 100 mg of wet tissue. Cervical vagotomy did not change the cyclic nucleotide concentration. To determine if there are adrenergic influences on cyclic AMP, we infused propranolol (1 mg per kg of body weight, intravenously) and observed a pronounced decrease in the level of cyclic AMP. This result suggests that the basal level of cyclic AMP in this part of the lung is stimulated by catecholamines. When we sectioned the sympathetic nerves to the lung, there was no change in cyclic AMP concentration; therefore, the effect of propranolol does not appear to result

from blockade of a sympathetic nervous effect on the basal level of cyclic AMP. Another possibility is that propranolol unmasks an alpha-adrenergic effect on cyclic AMP. Therefore, we infused propranolol and then administered an alpha antagonist (phentolamine), but this did not change the level of cyclic AMP. This suggests that the basal level of cyclic AMP in the lung must be slightly increased under our experimental conditions due to a circulating catecholamine, presumably released from the adrenal gland, stimulating beta-adrenergic receptors in the periphery of the lung.[7]

Effect of Histamine on Cyclic Nucleotide Metabolism

Histamine (0.05 mg per kg of body weight, given intravenously), an important mediator of anaphylaxis, was infused into the periphery of the lung through the pulmonary artery. Histamine caused a pronounced increase in both cyclic AMP and cyclic GMP; saline control infusion caused no changes in cyclic nucleotides. The increase in nucleotides occurred approximately two minutes after histamine was injected; however, airway smooth muscle contracted within 20 seconds after the bolus of histamine was infused *in vivo*. Clearly, changes in cyclic nucleotides must be secondary events. This conclusion is substantiated further by studies of the mechanism of the response to histamine. The usual response to histamine administered as a bolus intravenously is an increase of both cyclic nucleotides, a contraction of airway smooth muscle indicated by the increased total lung resistance and decreased static lung compliance, and a decrease in arterial blood pressure. When an antihistamine (chlorpheniramine, an H_1-antagonist) was administered before the histamine, there was a qualitative change from the usual response: both the increase in cyclic nucleotide levels and contraction of airway smooth muscle were prevented. The effect on smooth muscle in the cardiovascular system was only partially inhibited because, as already mentioned, this reaction to histamine depends on H_2-receptors, as well as H_1-receptors. We also examined the effect of indomethacin on this reaction. We chose indomethacin because previous workers have suggested that contraction of smooth muscle in the lung causes the release of prostaglandins; we speculated that the secondary rise in cyclic nucleotides was related to the contraction of smooth muscle induced by histamine, as suggested by Stoner and co-workers[9] and Andersson and associates[10] *in vitro*. After treating the animals with indomethacin, there was a notable difference in their response to histamine: the increase in cyclic AMP was completely blocked, but there was still a late rise in cyclic GMP, and airway smooth muscle contracted, as it did without indomethacin. Thus, not only does the time course of the response of the cyclic nucleotides to histamine suggest that their rise is secondary, but this pharmacologic experiment indicates clearly that the increased cyclic AMP is dependent on stimulation of prostaglandins, either by histamine directly, or by histamine-induced contraction of smooth muscle.[7]

Nervous Mechanisms in IgE-Mediated Reactions

In addition to these biochemical mechanisms involved in regulating the respiratory response to antigen, there are also important neural mechanisms involved. DeKock and associates[11] showed that when histamine was injected directly into the bronchial circulation of dogs, there was a progressive increase in airflow resistance. When the same experiment was done with conduction in the vagus nerves blocked, the reaction to histamine was notably inhibited. There was a direct, local effect, indicated by the 100 percent increase in resistance induced by 500 μg of histamine when the vagi were blocked. But in the presence of intact vagus nerves, there was an eightfold amplification of the reaction to the same dose of histamine. Therefore, we studied the role of the vagus nerves in modulating the response to antigen in our allergic dogs. Our hypothesis was that one amplification system of the antigen-antibody reaction is chemical and involves direct local effects on airways; another amplification system involves reflex mechanisms in vagal cholinergic pathways. Figure 7 is a tantalum bronchogram in which the airways were visualized with an inert radiopaque dust and the lungs were divided by a Carlen catheter. When we delivered antigen to the left lung only, not only did the left lung constrict, but the right lung constricted as well. Thus, bilateral constriction of the airways resulted when we challenged one lung only.[12] The effect of blocking the left vagus innervating the lung which received the antigen is shown in Figure 8. After antigen was delivered to the left lung, airflow resistance increased not only in the left lung but also in the right lung. When we cooled the left vagus nerve, blocking afferent signals conducted in it, the increased resistance was inhibited not

only in the left lung but also in the right lung. When we rewarmed the left vagus nerve, the action recurred bilaterally. We conclude that the antigen-antibody reaction in the left lung released mediator which stimulated sensory nerve endings in the left vagus, sending afferent signals to the central nervous system and efferent signals were transmitted in the right vagus nerve, producing the reaction observed in the right lung. The local, direct effects of mediators are indicated by the height of the bars during vagal cooling; the neural amplification by the height of the bars when the vagus nerves are both at 37°C.

Summary

The reaction immunologically mediated by antigen and IgE-antibody involves mast cells and their release of mediators (see Figure 9). These include preformed chemicals such as histamine, and the initiation of the synthesis of unstored mediators, such as slow-reactive substance, which can have direct, local effects on the airway smooth muscle. In addition to this local effect, sensory nerve endings within the airway are stimulated with afferent signals carried in the vagus nerves to the central nervous system and efferent signals carried in the vagus nerves to the smooth muscle, resulting in further amplification of the reaction. Our present experiments are designed to examine the effect of modulating this process by vagal-parasympathetic mechanisms as well as by sympathetic nervous and circulating humoral mechanisms. These experiments should clarify many of the biochemical and nervous mechanisms that

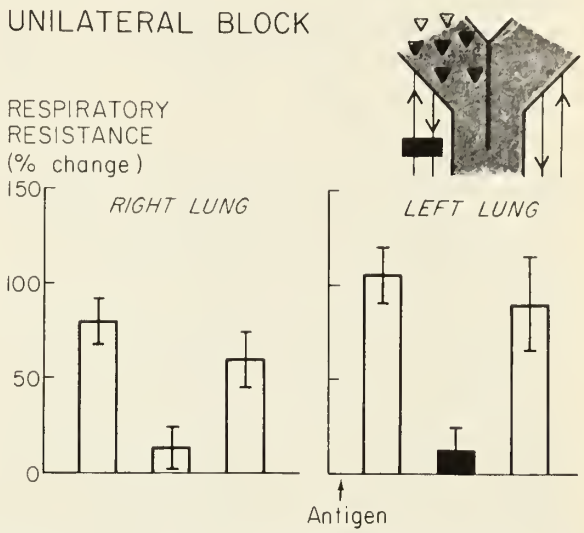

Figure 8.—Effect of ipsilateral vagal blockade on bilateral bronchoconstriction induced by unilateral antigen inhalation. Antigen aerosol was administered to the left lung only as indicated by the triangles in the diagram and the arrow in the right lower panel. Respiratory resistance is expressed in percentage change from control. The height of the bar indicates the mean response ±SE (I) in five dogs. Open bars: vagus nerve at 37°C before and after cooling left vagus nerve. Solid bar: left vagus nerve at 0°C. (Reproduced from Gold[1] with permission from Academic Press, Inc.)

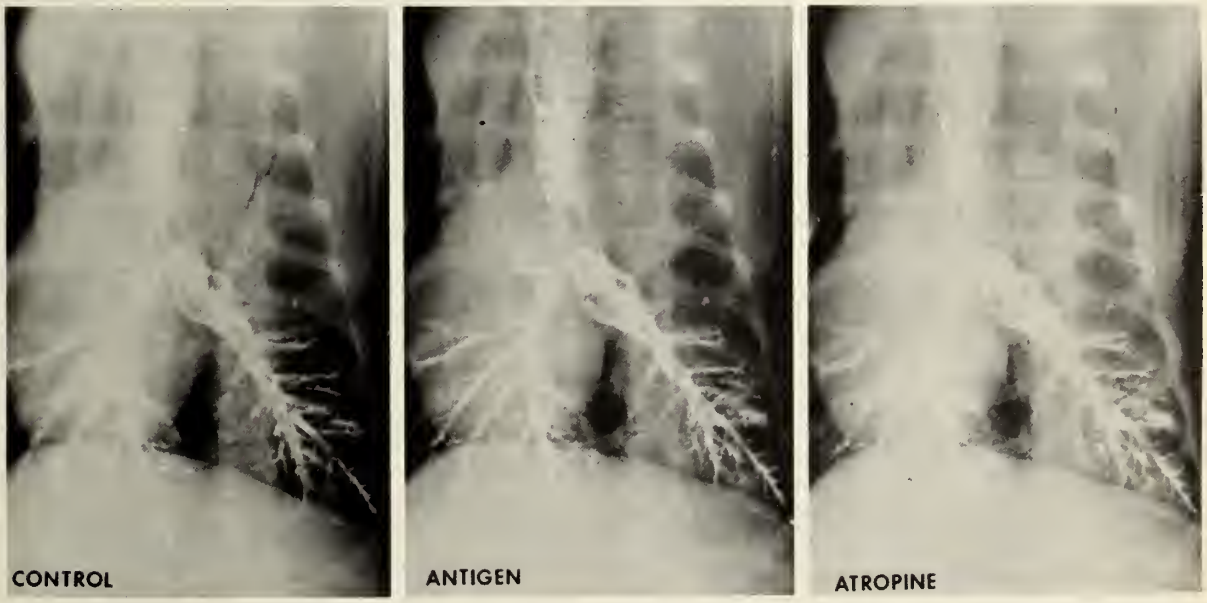

Figure 7.—Tantalum bronchograms showing effect of unilateral antigen inhalation. Control, localized bulges in walls of trachea and left main bronchus can be seen due to balloons on the Carlen catheter. After antigen aerosol inhalation by the left lung only, bilateral bronchoconstriction occurred. After atropine sulfate given intravenously, bronchoconstriction was inhibited in both lungs. (Reproduced from Gold, et al[12] with permission from J Appl Physiol.)

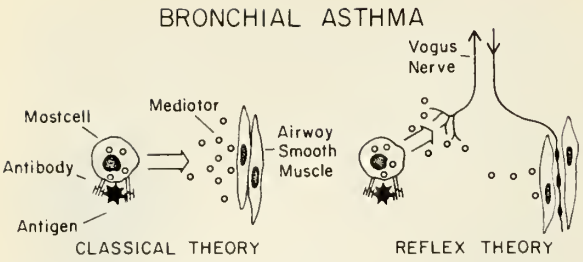

Figure 9.—The classical theory of asthma **(left)** suggests that antigen interacts with cell-fixed antibody to induce mediator release. The mediators of anaphylaxis, in turn, cause direct, local airway smooth muscle contraction. The concept cannot account for our results in experimental canine asthma or the accumulating evidence from experiments in anaphylaxis as well as human asthma. The classical concept must be modified as indicated on the right. Antigen-antibody interaction may cause mediator release with direct, local contraction of the airway smooth muscle. But in the acute response to inhaled antigen vagally-mediated bronchoconstriction also occurs. This reflex may result from stimulation of sensory receptors by the mediators, stimulation of the receptor by the antigen-antibody interaction itself, or stimulation secondarily after the mediators cause smooth muscle spasm and deformation of the receptors. Whatever the mechanism, it is clear that the parasympathetic nervous system is of central importance in the acute bronchoconstrictor response to inhaled antigen. (Reproduced from Gold[1] with permission from Academic Press, Inc.)

modulate the reaction between antigen and IgE-antibody.

Airway Hyperirritability

DR. NADEL:* Classically, asthmatic bronchospasm has been thought to be due to the direct effects on airway smooth muscle of mediators such as histamine released as a result of the reaction of inhaled antigens with specific antibodies fixed to sensitized mast cells. However, this simple explanation of asthma does not adequately explain many aspects of the disease.

For example, in healthy subjects, delivery of mediators (such as histamine, prostaglandins, serotonin) does not result in asthmatic-type bronchoconstriction. Delivery of the same mediators to asthmatic subjects results in dramatic airway narrowing.[13] These differences suggest that mechanisms exist in asthma whereby responses are magnified. We suggest that this "magnification" of response or "positive feedback" system is an important primary mechanism in asthma.

Further evidence that immunologic release of bronchoactive mediators is an inadequate explanation for the clinical findings in asthma derives from observations in allergic patients: Patients with atopic rhinitis may respond with bronchoconstriction to inhaled aerosols of specific antigen but do not have clinical evidence of asthma. We suggest that the presence or absence of asthma in these allergic patients is determined by whether the "positive feedback" system exists in the airways. Even in allergic ("extrinsic") asthmatic patients, clinical attacks usually correlate poorly with exposure to allergens. Moreover, many adult asthmatic patients have no evidence of allergic disease (hence the name intrinsic asthma). In patients with both extrinsic and intrinsic asthma, clinical attacks are usually triggered by nonantigenic stimuli, such as cold air, inhalation of irritating chemicals and dusts, exercise, and respiratory maneuvers (such as laughing, coughing, crying, hyperventilation). The tendency of patients with asthma to develop bronchoconstriction to a greater extent in response to smaller doses of various stimuli (including bronchoactive mediators) is an important characteristic of all asthmatic patients. The fact that the increased responsiveness to cold air, respiratory maneuvers, aerosols of histamine and citric acid,[13] aerosols of methacholine,[14] prostaglandin $F_{2\alpha}$,[15] and aerosols of surfactant and propellant[16] is abolished by atropine and by other anticholinergic drugs indicates that cholinergic postganglionic pathways are involved. We have suggested that the exaggerated response occurs via a vagal nervous mechanism.[13,17] Because the various stimuli that cause an increased bronchomotor response stimulate the rapidly-adapting receptors that are believed to lie immediately beneath tight junctions between airway epithelial cells,[18] we have suggested that damage to the airway epithelium could sensitize these sensory receptors, causing increased bronchoconstriction via a vagal reflex.[13,17] In asthmatic patients, damage to the airway epithelium might be due to inflammatory changes associated with an immunologic response (such as in extrinsic asthma), an infectious process (for example, "asthmatic bronchitis") or could be due to damage with other causes (such as respiratory viruses, inhaled pollutants[19,20]).

If airway epithelial damage is fundamental to the increased responsiveness of airway smooth muscle, then even subtle and reversible epithelial damage might cause a transient increase in bronchomotor responsiveness in otherwise healthy subjects. Damage to the airway epithelium can be produced

*Jay A. Nadel, MD, Professor, Department of Medicine.

by relatively low concentrations of ozone.[21,22] Anatomic studies indicate that the damage to the airways is maximal in 24 hours, and the airway epithelium heals within one to two weeks. Therefore, we exposed five dogs to ozone (0.7 to 1.2 ppm for two hours), and studied the effect of inhaled histamine sulfate aerosol (2 percent solution; five breaths delivered from a DeVilbiss #40 nebulizer). We evaluated the effect of histamine on the airways by measuring total pulmonary resistance to airflow (R_L). In each of the five dogs 24 hours after ozone exposure, the baseline R_L was unchanged, but the increase of R_L caused by histamine aerosol was greater than in the control state (Figure 10). This transient state of increased bronchial responsiveness was maximal 24 hours after exposure to ozone (the time when evidence of anatomic damage was greatest) and returned to control levels gradually over 7 to 28 days.[23] To test our hypothesis that cholinergic pathways were involved in the ozone effects, we pretreated the dogs with atropine sulfate aerosol (1.5 percent solution; ten breaths). Atropine did not affect the baseline R_L significantly, either before or after ozone exposure, but abolished the increased bronchomotor response to histamine after exposure to ozone (Figure 11, upper panel). Since

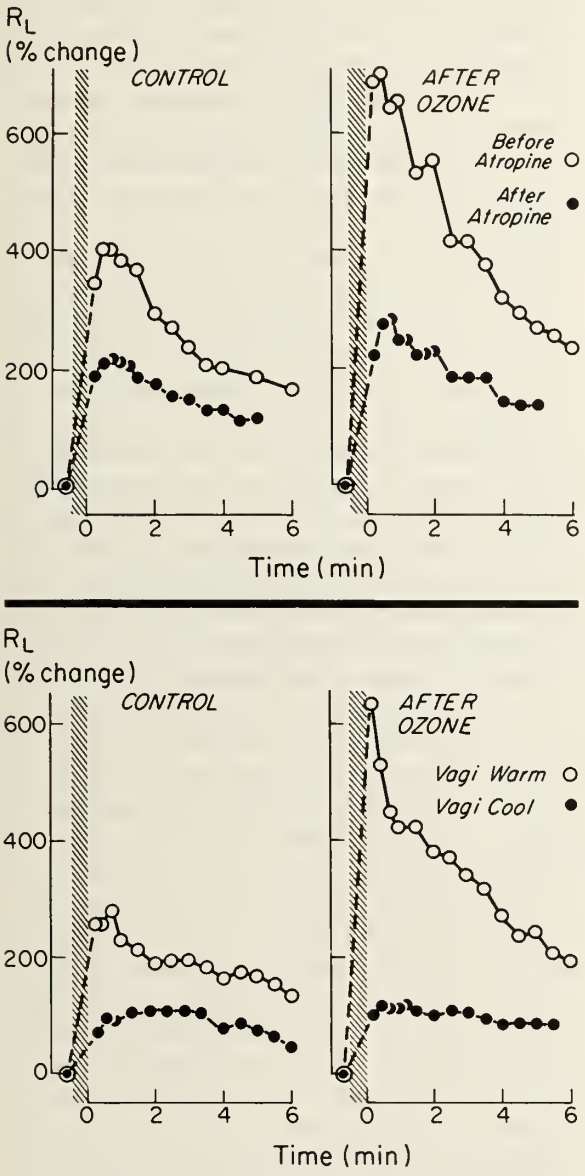

Figure 10.—Effect of inhaled histamine aerosol (five breaths of a 2 percent solution) (shaded bar) on total pulmonary resistance (R_L) in one dog, before ozone **(left)** and after ozone **(right).** Each point is the mean of three to five determinations. (o—o) = before intervention. **(Upper panel)** (•—•) = After inhalation of atropine sulfate aerosol (ten breaths of a 1.5 percent solution). **(Lower panel)** (•—•) = During cooling blockade of the cervical vagus nerves to −2°C. (Reproduced from Nadel[33] with permission from Am Rev Resp Dis.)

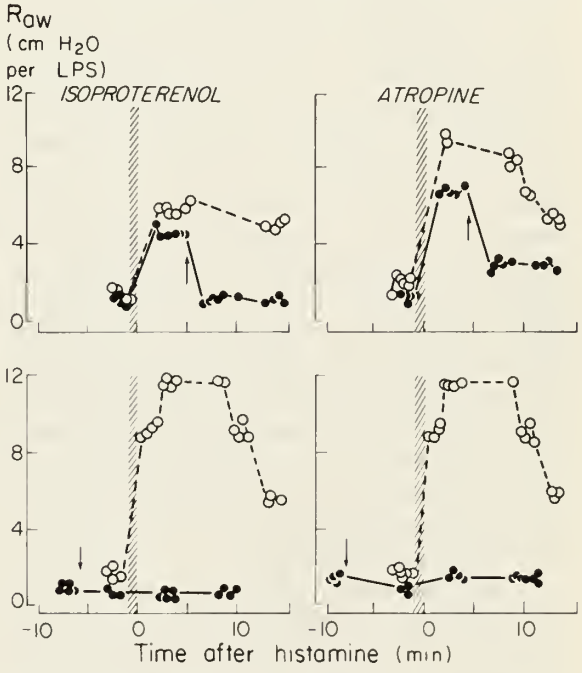

Figure 11.—Effects of isoproterenol (0.5 percent, one breath; left panels) and atropine (0.2 percent, 20 breaths; right panels) on airway resistance (R_{aw}) after inhalation of histamine aerosol (1.6 percent, ten breaths; shaded bars) by human subjects with colds. Each panel shows the effect of histamine alone (o) and after administration of isoproterenol or atropine (at the arrows, •) in the same subject. Upper panels show the effects of isoproterenol and atropine in reversing the effects of histamine; lower panels show the same drugs preventing the responses to histamine. The arrows indicate the time at which atropine or isoproterenol was administered. (Reproduced from Empey[19] with permission from Am Rev Resp Dis.)

the vagus nerves provide the cholinergic innervation of the airway smooth muscle, we studied the effect of blocking conduction in the vagus nerves. Cooling blockade of vagal nervous conduction abolished the increased bronchomotor response to histamine after ozone exposure (Figure 11, lower panel).

Histamine has two effects on bronchomotor tone. It can act locally on airway smooth muscle to cause contraction;[24] it can also stimulate vagal sensory receptors in the airways and cause reflex bronchoconstriction.[11] Since the increased responsiveness of the airways to inhaled histamine after ozone exposure was abolished by atropine and by blocking conduction in the vagus nerves, the increased response was due to potentiation of the reflex, not the local response.

Because viral respiratory tract infections also cause transient damage to the airway epithelium, we studied the effect of inhalation of histamine aerosol (1.6 percent solution; ten breaths) on airway resistance (R_{aw}) in otherwise healthy subjects with colds.[19] In 16 normal subjects with colds, baseline R_{aw} was not significantly different from eleven healthy control subjects. However, inhalation of histamine aerosol produced a greater increase in R_{aw} in the subjects with colds compared to the control group. The increased bronchial responsiveness appeared within two or three days after the onset of the cold and returned to normal in variable periods up to seven weeks. Because of the difficulties in timing the onset of spontaneous viral infections and in determining their exact causes, we also studied in a double-blind manner the effect of live attenuated influenza virus (Alice strains of influenza A and B virus; Smith Kline & French) delivered into the airways. We monitored bronchial response to inhaled histamine in healthy subjects with hemagglutination-inhibition antibody titers of 1:8 or less to homologous influenza A virus. Subjects who received placebo showed no change in the response to inhaled histamine aerosol, but subjects who received virus and who subsequently developed greater than four-fold rises in hemagglutination antibody titers showed increased bronchomotor responses to inhaled histamine compared to their control states. Bronchial responsiveness was maximal on the second day and disappeared by the ninth day after administration of virus. Atropine sulfate aerosol (0.2 percent solution; 20 breaths) abolished the increased bronchomotor response to histamine in subjects with spontaneous colds (Figure 11) and in subjects inoculated with live attenuated influenza virus.[25]

Exposure to ozone and respiratory viral infections both cause transient damage to the airway epithelium, and we suggest that this damage is the cause of the transiently heightened bronchial responses to inhaled histamine aerosols. The fact that, in each case, the increased responses were abolished by blockade of conduction of the vagus nerves and by atropine sulfate (a drug whose major effect is to block postganglionic cholinergic pathways) is compatible with our hypothesis that damage to the airway epithelium exposes sensory nerve endings and potentiates reflex bronchomotor responses.

Stimulation of sensory nerve endings in the conducting airways causes reflex bronchoconstriction, but these sensory pathways also have other central nervous connections and thus cause other reflex responses (such as cough, rapid, shallow breathing).[26] Thus, the threshold concentration of an inhaled irritant (citric acid aerosol) required to produce cough decreased during respiratory viral infection,[19] and this provides further evidence that sensitization of nerve endings occurs when airway epithelial damage occurs. The rapid, shallow breathing pattern observed after inhalation of ozone[27] may also be due to oxidant damage to the airway epithelium with subsequent effects on vagal nerve endings and reflex stimulation of ventilation. In fact, the chronic respiratory alkalosis in asthma[28] and even the sensation of dyspnea perceived by asthmatic patients may be due to abnormal stimulation of nerve endings in the airway epithelium.

Studies of the pathogenesis of asthma have concentrated on the airway smooth muscle and on mast cells. Our hypothesis is that damage to the airway epithelium plays an important primary role in asthma. Therefore, we suggest that: (1) In atopic patients in whom bronchoconstriction develops following inhalation of specific antigen, the presence or absence of clinical bronchospastic disease may depend on the presence of airway epithelial damage. (2) In intrinsic asthma, mediators may be released from cells other than mast cells (for example, leukocytes, macrophages, platelets). In this case (as with extrinsic asthma), epithelial damage sets up the "positive feedback" system that allows clinical bronchospasm to become evident. (3) Our studies on respiratory viruses in healthy subjects provide a mechanism

by which viral infections precipitate asthmatic attacks[29,30] and cause exacerbations of chronic bronchitis.[31] (4) Ozone has reached ambient levels as high as 0.54 ppm in Los Angeles and in other cities. Consequent damage to the airway epithelium that occurs at these concentrations[21] could affect airway function deleteriously, especially in patients with pulmonary diseases (such as asthma). (5) Mucous glands receive cholinergic innervation,[32] and application of cholinergic agonists to the airways stimulates secretion.[33] The mucous hypersecretion that may occur in asthmatic patients could be due to cholinergic reflex pathways (potentiated by sensitization of the sensory pathways). Both smooth muscle and mucous gland hypertrophy that occur in asthma and in chronic bronchitis may be due to chronic reflex overstimulation.

Mucociliary Clearance

In some asthmatic patients progressive bronchial narrowing develops, relatively unresponsive to bronchodilator drugs. Some investigators have suggested that this narrowing is due to continued smooth muscle contraction that has, by continued use, become resistant to beta-adrenergic drugs. However, postmortem examination of the airways in such patients shows there to be obstruction of airways due to inspissation of mucus. Respiratory tract fluid is secreted into the airway lumen and then propelled up the airways by ciliary action. Clearance of inhaled insoluble particulate material is determined by the interaction of ciliary motility and the physical properties of the mucous blanket. Water lubricates the airways and facilitates coupling between mucus and cilia by forming a layer through which the cilia move to propel mucus toward the mouth. Abnormal clearance from the airways in disease (such as in status asthmaticus and cystic fibrosis) may be due to a loss of normal water flow into the airway lumen. Since water flow is linked to active ion transport in other epithelia, we set out to determine whether such active transport of ions exists in the airway epithelium. To accomplish this, we applied Ussing's short-circuit technique to canine airway epithelium *in vitro*.[34] We anesthetized dogs, excised the trachea, dissected off the trachealis muscle and mounted the posterior membranous portion of the remaining epithelium between the two halves of an Ussing chamber. We measured electrical potential difference and short-circuit current via two electrical circuits connected to the chamber by agar bridges. We used radioisotopes (^{22}Na, ^{24}Na, ^{36}Cl) to measure unidirectional ion fluxes. We found a stable potential difference (30.7 ± 1.7 mV) lumen negative to submucosa; and a stable short-circuit current (108 ± 8 μA per sq cm). These findings suggested the presence of an active ion pumping mechanism across the airway epithelium. We confirmed this by finding a net flux of Cl^- toward the lumen (2.7 ± 0.6 μEq per sq cm per hour) and a net flux of Na^+ toward the submucosa (0.8 ± 0.2 μEq per sq cm per hour).

This net transport of ions toward the airway lumen could provide a mechanism for regulating water flow. Because furosemide inhibits Cl^- transport in the thick ascending limb of the nephron, we studied the effect of this drug on Cl^- transport across the airway epithelium.[35] Furosemide inhibited Cl^- transport when the drug was added to the submucosal side, but not when it was added to the luminal side of the epithelium. These findings suggest that the Cl^- pump is located on the submucosal side of the epithelium.

Several pharmacologic agents important in asthma have significant effects on epithelial ion transport in airways. Histamine, a mediator of the allergic response of airways, increased the net ion flux of Cl^- toward the lumen, a response that was inhibited by diphenhydramine, but not by burimamide, suggesting that this effect of histamine is via a H_1-receptor.[36] Acetylcholine, the mediator released at postganglionic vagal nerve endings, also increased net flux of Cl^- toward the lumen,[37] and this provides a mechanism whereby water secretion could occur in response to cholinergic stimulation. Hypersecretion may be a part of the reflex that occurs in response to mechanical, chemical and pharmacological stimulation of the airways in asthma. Beta-adrenergic agonists are known to have beneficial therapeutic effects in asthma. In addition to their bronchodilator effects, these agents increase Cl^- flux toward the airway lumen,[38] and this effect may be the mechanism whereby mucociliary clearance is improved.[39] Our studies have shown an active ion transport mechanism whereby water transport may be regulated normally in the airway epithelium. Inhibition of ion transport may occur in some asthmatic patients and may lead to abnormal mucociliary clearance and inspissation of mucus that occurs in status asthmaticus. Drugs affecting ion transport may provide a rational basis for therapy in these patients.

Airway epithelium is made up of multiple types of cells (such as ciliated cells, goblet cells, mucous gland cells). A study of regulation requires isolation of each of these biological subunits. Because of their size, submucosal glands are likely to be major contributors to total airway secretion, and we are developing techniques for their study.[33] In anesthetized dogs, we incised the anterior surface of the trachea, pulled the edges widely apart to expose the epithelial surface which we visualized through a dissecting microscope. Since no landmarks exist to locate the gland duct openings, we deposited a fine layer of powdered tantalum on the surface to prevent the normal dispersion of fluid on the surface. Anatomic studies suggest that cholinergic nerves innervate the glands.[32] When we stimulated the vagus nerves electrically, elevations appeared in the tantalum layer due to accumulation of submucosal gland fluid (Figure 12). We proved that the elevations were located above mucous gland duct openings by fixing the tissue and gently removing the elevations: Duct openings were present over each removed elevation (Figure 13). We can now remove fluid from individual gland ducts with micropipettes and can study their regulation by techniques analogous to study of the nephron. These techniques should allow a better understanding of the role of the mucous glands in the regulation of normal airway secretions and the effects of various interventions.

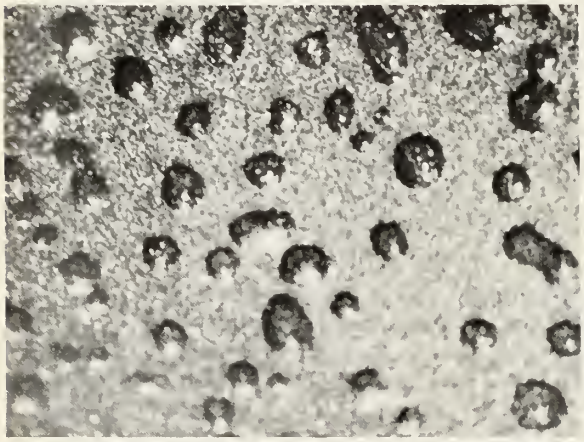

Figure 12.—Photograph of exposed canine cervical tracheal epithelium obtained through a dissecting microscope. The epithelium was coated with powdered tantalum, and the cervical vagus nerves were stimulated to produce elevations (hillocks) due to accumulated secretions. (Reproduced from Nadel[33] with permission from Am Rev Resp Dis.)

Figure 13—Photograph of gland duct openings in exposed canine epithelium obtained through a dissecting microscope. After the tracheal epithelium was coated with powdered tantalum and the vagus nerves were stimulated to produce secretory elevations, the trachea was fixed with Bouin solution, and hillocks were removed with a fine cotton swab. Photograph shows gland duct openings (black dots, approximately 30 mm in diameter) surrounded immediately by a circular area (approximately 300 μm) of removed secretions. Dark intervening surface of tracheal epithelium is covered with tantalum powder.

Summary

In this review we have summarized current concepts in the biology of IgE, the roles played by mast cells, chemical and nervous mechanisms involved in IgE-mediated reactions, a new hypothesis explaining airway hyperirritability and, finally, mechanisms controlling mucociliary clearance in airways. We believe that our understanding of the pathogenesis of asthma will be improved by these advances, but also that they will provide a basis for developing improved therapy of patients with this disease.

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Cold Sterilization Techniques and Hepatitis B

YOU CAN GET HEPATITIS at our major department stores if you go in to get a free ear-piercing. The ear-piercing instrument, invariably, is cleaned by alcohol which has absolutely no effect against hepatitis B virus. And if by chance the ear piercer pierces the ear of someone who has hepatitis, or in whom hepatitis is incubating, or who is a carrier of hepatitis, it is easy then to transmit it to the next earring purchaser.

—GARY L. GITNICK, MD, *Los Angeles*

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Important Advances in Clinical Medicine

Epitomes of Progress—Orthopedics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in orthopedics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in orthopedics which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Orthopedics of the California Medical Association the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Electrical Stimulation in Bone Healing

DURING THE LAST 20 YEARS investigators have shown that the application of small amounts of electric current to bone stimulates bone formation at the site of the negative electrode or cathode. Recent clinical trials in patients with long-term nonunions have shown a healing rate of approximately 70 percent with the use of electric current. There has also been some success with healing of congenital pseudarthrosis of the tibia in children—a condition which in the past frequently necessitated amputation.

Three different methods are in clinical experimental use at present:

(1) A totally invasive method where the coiled negative electrode is placed within the nonunion site and the battery and positive electrode or anode are buried in the surrounding muscle. This requires an anesthetic and an open surgical procedure.

(2) A semi-invasive technique where several small K-wire electrodes are placed percutaneously into the nonunion site and the battery and anode are external to the skin and incorporated in the cast.

(3) A noninvasive technique where an electromagnetic field is produced by applying a coil to the exterior of the cast. This has the advantage of not requiring surgical operation but it is more difficult to focus the current flow directly to the nonunion site. All methods have been shown to increase the formation of bone.

The basis for this research was the previous finding that piezoelectric behavior is an inherent property of bone. Piezoelectricity may be defined as electricity resulting from pressure on crystals.

There are two types of electric potentials normally produced in bone:

(1) Mechanical stress-generated potentials that are electronegative in areas of compression and electropositive in areas of tension. These are present even when bone is not living. These potentials are a major factor in remodeling of bone along lines of stress both in growing children and in adults after fracture.

(2) The second type are called nonstress generated potentials. These are present even when bone is not stressed and are dependent on living bone cells. These potentials are responsible for the growth plate in a long bone being electronegative during growth. The diaphysis or shaft of a long bone is normally electropositive but turns electronegative when a fracture occurs and remains so until the bone is healed.

Basic research is now being done to attempt to

elucidate the link between electricity and change in biologic behavior of bone. At present the evidence suggests that electricity may produce an increase in the cyclic adenosine monophosphate production within the bone forming cells which may stimulate an increase in bone formation.

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The Use of Large Osteocartilaginous Allografts for the Replacement of Segmental Defects in Orthopaedic Surgery

LARGE MUSCULOSKELETAL ALLOGRAFTS have been used since the early 1900's; however, now there is renewed and growing interest in this particular procedure. With the development of antibiotics, better methods of internal fixation, and newer techniques in tissue banking and tissue transplantation, the success rate of musculoskeletal allografting has improved considerably. Over the past decade, in more than 200 cases locally aggressive tumors have been resected and the bony defect replaced with a musculoskeletal allograft. At the time of placement of the allograft bone in the recipient, large additional autograft bone from the iliac crest is usually placed inside the allograft bone as well as around the osteosynthesis sites. This technique has been shown in experimental animals to improve greatly the eventual incorporation of the donor bone by the recipient. The donor bone is known to be dead as it is placed into the recipient, however, it is eventually replaced by living bone of the recipient. This process is one that takes many months to several years, and is usually best followed by the gradually increasing activity shown on bone scan followed by a decline to normal activity.

Joint deterioration has always been a problem since the beginnings of allografting, and is thought to be due to three possible mechanisms: (1) poor fit of the donor joint surface to the recipient joint surface when only half a joint is being replaced, (2) the fact that methods of preservation of the musculoskeletal allograft (such as freezing) usually destroy the cartilage cells which do not regenerate after implantation and (3) an immune response gradually taking its toll in the form of a pannus-like destruction of the joint surface. In an attempt to improve the results due to the detrimental effects of the above factors, the following procedures are being carried out. First, a good fit is obtained by selecting an x-rayed graft segment that will fit the recipient surface, and in any areas of misfit, trimming of the graft tissue is done to obtain as good a fit as possible. Second, new methods of cryopreservation are being used by exposing the cartilage during freezing to 10 percent dimethylsulfoxide (DMSO) in order to store the cartilage in a viable state. It is to be hoped that this immunologically privileged tissue will remain viable after transplantation. Third, new methods are being investigated to decrease the immune response against the specific tissue being transplanted. Attempts have not been made to obtain an identical histocompatibility antigen (HLA) match, because the chances of doing so are less than 1:150,000. Instead, attempts at decreasing the antigenicity of the musculoskeletal allograft are being carried out, such as removing as much of the marrow as possible and storing the graft at $-80°C$.

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Ender Nail Fixation for Intertrochanteric Hip Fractures

OPERATIVE TREATMENT of intertrochanteric fractures of the femur in adults has become generally accepted as the preferred form of management. Patients with these injuries are usually elderly, are often debilitated, and withstand poorly the three months or so of bedrest and traction required to achieve a stable union. Surgical treatment, however, confers its own risks and problems. Many variations on the theme of nail and side plate have been proposed for fixation of intertrochanteric fractures, but they all require a substantial lateral exposure of the proximal femur. The fracture is rendered susceptible to infection. Operative blood loss is often significant and secure fixation is not always obtained. Therefore, postoperative traction or reoperation are occasionally required.

Because of these problems, interest remains in developing alternative approaches to the management of intertrochanteric hip fractures. Ender

has proposed the use of multiple, flexible, prebent steel nails, inserted intramedullarly just above the medial femoral condyle. From this site, just above the knee joint, the nails are advanced one at a time along the medullary canal, across the fracture and into the subchondral bone of the femoral head. Three to five nails are used, to gain multiple points of fixation. The procedure is done on a fracture table, using traction to align the fracture, and it requires the use of a c-arm fluoroscope, preferably with a disc recorder to minimize radiation exposure. The incision is distant from the fracture, and requires less exposure and blood loss. The nails are placed along the lines of stress of the proximal femur, and are less likely to fail. However, they do occasionally back out. Subsequent external rotation of the fracture can occur. Knee pain, related to the site of insertion, is an acknowledged problem.

Ender's procedure does appear, however, to be very successful in permitting a patient with an intertrochanteric fracture to be up and walking shortly after injury, with a much less invasive operation than conventional hip nailing. Ability to work does not seem compromised.

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New Methods In Treating Femoral Shaft Fractures

NEW METHODS in treating femoral shaft fractures have greatly reduced the expense and disability of this injury. These methods include the use of a quadrilateral cast brace and closed medullary nailing.

A quadrilateral cast brace utilizes some principles of a quadrilateral above knee prosthesis to control the position of the proximal fragment and allow early knee motion and ambulation of the patient. The cast may be applied after clinical stability is achieved with skeletal traction, or, in some selected cases, it may be applied and the patient allowed to move about before clinical stability of the fracture.

Closed medullary nailing requires sophisticated and expensive equipment but allows internal fracture stabilization without exposing the fracture site and, therefore, greatly reduces the risk of infection. Properly done, fixation is usually secure enough to allow full weight-bearing without protection soon after the soft tissues have healed. Patients frequently resume most of their normal activities within four to six weeks after the procedure.

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Reconstruction of Bone Defects by Free Vascularized Bone Grafts

WITH RECENT ADVANCES in clinical microsurgery, free vascularized bone grafts to fill defects in long bones are now possible. Defects created by trauma or resection of bone for tumors have been filled by free vascularized grafts and reported by Weiland and Daniel.

The three donor bones used for free microvascular transfers are the fibula, rib and iliac crest. All bones are transferred on a vascular pedicle that is anastomosed by microvascular technique to vessels at the recipient site. The anatomic vascular arrangement has been studied in cadavers for each of these donor grafts. However, the authors recommend preoperative angiograms to define the vascular pattern in each individual case. The fibula is transferred with the peroneal vessels which are readily identified with microvascular technique and the rib grafts are vascularized by the intercostal vessels. The iliac crest has usually been transferred as part of a composite tissue-free groin flap vascularized by the superficial circumflex iliac and inferior epigastric vessels. Where only bone is necessary and particularly where long defects need to be filled, the fibula is the most suitable donor bone.

If the vascular anastomosis fails, the bone graft is no worse than a traditional free bone graft without a vascular pedicle. It has been shown, however, that the vascularized bone grafts heal faster and the nonunion rate will be less. Of the 13 cases reported, nine bony defects were due to trauma and four were created following bony resection for locally aggressive or malignant lesions.

Microvascular surgery has opened up this new reconstructive technique which may allow less

radical surgical procedures to be done in locally aggressive and malignant bone tumors as well as heal traumatic defects in long bones more predictably.

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The Use of Transcutaneous Doppler Ultrasound in Predicting Healing Potential and Selection of Surgical Levels in Dysvascular Lower Limbs

TRANSCUTANEOUS DOPPLER ULTRASOUND has been used at Rancho Los Amigos Hospital to determine healing and surgical levels in dysvascular lower limbs. The Doppler probe is used as a sensitive stethoscope to map the arterial tree and to determine systolic blood pressures. Carter pointed out that healing of skin lesions was poor in diabetic and nondiabetic patients if the systolic pressure was less than 55 mm of mercury. The prognosis was good if pressures were above 70 mm of mercury. We have extended this use of Doppler pressures by comparing the lower extremity pressure with that of the upper extremity. The Doppler technique is of particular value as it allows blood pressures to be taken that cannot be heard with the standard stethoscope in the dysvascular lower limb.

Systolic pressure is measured in the brachial artery, at the upper, middle and lower thigh, at the upper and middle leg, at the ankle and midfoot and in the toes. Frequencies between 9 and 10 MHz appear to be more satisfactory for the smaller vessels in the toe and midfoot. The width of the sphygmomanometer cuff should be 120 percent of the width of the extremity at the site being measured.

An ischemic index is calculated by dividing the lower extremity pressure by the brachial artery pressure. The brachial artery is considered normal for that patient's particular physiological processes and the index is thus usually 1 or a fraction thereof. For example, if the pressure is 120 in the arm and 60 at the knee, the ischemic index at that level would be 60/120 or 0.5. For a pressure of 30 at the midfoot, the index would be 30/120 or 0.25. The healing level is predicted in diabetic persons where the index is at least 0.45 and in nondiabetic persons where the index is at least 0.35. In addition, the systolic pressure should be at least 70 mm of mercury and the flow should be pulsatile.

The usual case seen is that of a 55-year-old diabetic patient with an open ulcer on the foot that has not responded to local treatment. Nonoperative procedures such as intravenous administration of antibiotics, local treatment with organic iodine complexes and Collen triple iodide solution, walking casts and similar treatments are begun. Lesions that do not heal are then treated surgically.

In all, 377 consecutive lower extremity surgical procedures were carried out from January 1975 to May 1978. There were 314 diabetic and 63 nondiabetic patients. Surgical procedures included incision and drainage of superficial to deep abscesses, toe and partial foot amputations, and major amputations including Syme, below knee, through knee and above knee. There was healing in 92 percent of the diabetic and 97 percent of the nondiabetic patients for an overall healing rate of 93 percent. This contrasts notably with the approximately 70 percent healing rate which was obtained previously with clinical indicators such as temperature, leukocyte count, arteriography, and similar standard clinical evaluations for lesions in dysvascular lower limbs.

A transcutaneous Doppler ultrasound study is a noninvasive test and can be carried out as an outpatient test with relatively inexpensive portable equipment. The procedure should be added to the diagnostic armamentarium wherever amputations are done and lesions of the dysvascular lower limb cared for.

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Autologous Transfusions: Their Use in Spinal Surgery

AUTOLOGOUS TRANSFUSION is a safe and effective way of providing a patient with perfectly crossmatched blood that has minimal risk of disease transmission. Autologous transfusions have received increasing attention in recent years. We established a program of preoperative blood collection and storage for patients undergoing Harrington rod instrumentation for treatment of scoliosis. A study was done with 40 patients and

the results for 20 patients who participated in the autologous transfusion program were compared with those for 20 control patients. An average of five units of autologous blood was collected before operation from the participants. The average length of time from the first visit to the blood bank for phlebotomy to surgical operation was 8½ weeks. No patient came to surgery with an hematocrit of less than 30 percent. Complications associated with collection were minor and were related to transitory hypotension.

Of the 20 participants, 7 required no homologous blood and 13 required additional homologous blood. There were no complications associated with the transfusion of autologous blood. However, there was one patient who participated in the autologous blood transfusion program who did have a weak isoleucoagglutinin transfusion reaction upon receipt of a unit of homologous blood. Transfusion reactions developed in two patients in the control group; in one a weak cold agglutinin developed and in the other a weak isoleucoagglutinin reaction occurred.

The patients who participated in the program were predominantly young females undergoing extensive surgical procedures and requiring massive transfusions. The use of autologous blood reduced the risk of disease transmission, avoided hemolytic transfusion reaction as well as minor transfusion reactions, and reduced the risk of isoantibody sensitization, which might complicate future pregnancies. The use of autologous blood for transfusion reduces perioperative and postoperative morbidity and its wider application for elective orthopaedic procedures is recommended.

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Musculoskeletal Soft Tissue Masses

AN EXTREMITY MASS that is suddenly noted by a patient can be a perplexing and possibly serious problem. A few special studies may be helpful, but most of the important information can be obtained by a simple history, physical examination, x-ray films and basic laboratory studies. It is reassuring that most of all such suddenly appearing lumps are benign but since the individual odds are either zero or 100 percent (it is either a cancer or not) it is good practice to consider all of them malignant until proven otherwise.

Distinguishing a solid (probably neoplastic) mass from a fluid mass is most easily done by transillumination. Optimally, there must be time for dark adaptation and a shielded light source in a completely darkened room. If the mass does not brightly transilluminate, it is probably a solid tumor and a biopsy specimen must be taken without delay. The only solid tumors that transilluminate are lipomas and, occasionally, low-grade liposarcoma. Hematomas, although fluid, will not transilluminate. If the mass transilluminates, it should be aspirated for confirmation and specific studies, occasionally including the injection of water-soluable contrast material for a "cavitygram." If the mass is attached to the skin, particularly by a scar, it suggests an epidermal inclusion cyst. If the mass moves transversely but not in the long axis of the extremity, it suggests a tumor of a peripheral nerve. The consistency of a given mass is not of diagnostic importance and the old aphorism that "cancer is hard" is not reliable. Rapidly growing tumors tend to be soft because of hemorrhage or necrosis. Hemangiomas feel warm to the touch and may diminish in size on elevation of the extremity. Ganglia and cysts communicating with a joint may change in size with motion. If the tumor is in a muscled region, subfascial tumors are *less* palpable and subcutaneous tumors are *more* palpable when the muscle is tensed. Muscle hernias are more prominent on contraction and a fascial defect may be palpable on relaxation.

Biplanar x-ray studies can be supplemented with tangential soft tissue technique films using lead skin markers to delineate very simply the density and extent of the tumor. Specific densities may suggest the diagnosis; heavy flocculant calcification occurs in cartilage matrix and multiple spherical densities are often seen in hemangiomas. A lacy or trabecular pattern can be seen in heterotopic bone formation (myositis ossificans), and dusty calcification may be seen in synovial sarcoma. Low grade liposarcomas occasionally present with a rim of calcification at a portion of their periphery. Angiography helps delineate the extent of the mass, may differentiate infection from a vascular malignant tumor, and shows major vessels to the surgeon or radiologist for surgical planning, consideration of chemotherapy infusion, or embolization. Computerized axial

tomography is almost mandatory in the preoperative evaluation of extremity tumors and is most helpful in the design of muscle group resection or decision to amputate. Computerized tomographic lung examination is also the best way to search for metastatic pulmonary nodules.

Consultation with a surgical pathologist and a surgeon experienced in extremity surgical procedures is advisable before taking a biopsy specimen of a probable primary malignancy. An unconsidered biopsy study, particularly in a difficult location, may lead to excess blood loss and excessive regional dissemination of tumor cells, and may complicate the definitive en bloc resection of the biopsy tract or surgical scar with the major tumor.

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Management of Musculokeletal Sarcomas

SARCOMAS ARISING in the locomotor tissues are dangerous for several reasons. First, they are rare (less than one percent of all malignant lesions) so a high index of suspicion is necessary or else cancer will be forgotten in the differential diagnosis. Second, metastases tend to occur early and are difficult to discover. Third, these tumors have a pseudocapsule and are easily "shelled out," leaving a surface of raw tissue with residual tumor cells to find their way into the blood and lymph vessels. Fourth, manipulation and bleeding at the time of biopsy cause dissection along tissue planes which spread living tumor cells relatively far from the surgical site. Finally, they may become locally advanced before they cause enough symptoms to be noticed. When the tumor is discovered, an *immediate investigation* is in order since the tumor will have been present for a long time.

The first step is to establish the diagnosis with certainty. There are perhaps two dozen types of sarcomas of soft tissues each of which has its proclivities as to sex, body location, local aggressiveness, tendency to metastasize, response to treatment modalities and ultimate prognosis. Because mesenchymal tissues are derived from common stem cells, sarcomas may be quite primitive locally even when otherwise diffierentiated. There may even be different tissues in the tumor. The surgical pathologist then is often faced with a bewildering histopathological problem in diagnosis. Obviously, the rarity of these tumors affords maximum experience to only a few surgical pathologists. A frozen section examination is not realistic at the time of biopsy because consultation, special stains and occasionally electron microscopy may be necessary before diagnosis.

The second step determines the stage of the tumor: local, regional or distant. Angiography and computerized axial tomography are helpful in showing the extent of the tumor and its relationship to bone, nerve and blood vessels. Ultrasound imaging is less helpful. Lymphography is being studied but is as yet not proven to be useful in planning surgical therapy or radiotherapy. If routine x-ray films of the chest are negative, pulmonary computerized axial tomography will identify metastases less than a centimeter in diameter. Radionuclide bone scan is helpful in finding asymptomatic skeletal metastases. Liver and brain scans are optional, but have not proven helpful unless there is a specific indication.

Cancer persists in at least two thirds of local excisions and up to a third of patients who are managed by radical excision, depending on several variables. Radical local excision must include one full uninvaded tissue-plane from the tumor in all three dimensions. This may necessitate resection of bone or major muscles, amputation or skin grafting. Additionally, vascular or nerve resection and reconstruction will occasionally be mandated by clinical, angiographic, electromyographic or operative findings. External megavoltage radiotherapy may be advisable to sterilize any residual locally micropersistent tumor cells. Interstitial after-loading techniques using iodine 125 or iridium 192 may be helpful for macro-locally-persistent tumor, or to sterilize the tumor bed. Using this, the irradiation dose can be pushed to 10,000 rads in a small volume of tissue using this still-evolving technique. Adjuvant doxorubricin cycled with high dose methotrexate and citrovorum rescue, or with moderate dose methotrexate, have been shown to improve survival and disease free intervals in many of the soft tissue sarcomas. Other agents and combinations are also being used as adjuvant chemotherapy. Wound healing must be uncomplicated before initiating external irradiation or these medications and if

radiotherapy and chemotherapy are given simultaneously, modifications in dosages must be made or serious synergistic effects may occur. Development of a treatment program will usually require consultation among a surgeon, a radiotherapist and an oncologist.

Pulmonary macrometastases, although ominous, can be wedged-resected, with occasional satisfying prolongation of disease free intervals. Several lesions, even if bilateral, may still be amenable to resection. Failure of local control, rapid appearance of pulmonary lesions, or perhaps a rapid "doubling time" is a relative contraindication to this somewhat aggressive but occasionally rewarding palliative surgical therapy. The effects of manipulating the immune system are still unpredictable, but work is progressing in this difficult but intriguing area.

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The Use of Antibiotics in Open Fractures

UNTIL RECENTLY the use of prophylactic systemic antibiotics in open fracture treatment was a controversial subject with some published reports supporting their use and others finding them of little or no value.

In 946 open fractures treated at the Los Angeles County/University of Southern California Medical Center, we have found that bacterial contamination was present in approximately 63 percent of the open wounds cultured. The infection rate was significantly reduced by the use of an antistaphylococcal wide-spectum agent (cephalothin [Keflin]) in patients with open wounds (2.3 percent), when compared with a control group receiving no antibiotics (13.9 percent) and a control group receiving penicillin and streptomycin (9.7 per cent).

Based on these data, wide-spectrum systemic antibiotics should be used as an adjunct to surgical irrigation and debridement to treat contaminated wounds and reduce the incidence of infection. Wide-spectrum antistaphylococcal systemic antibiotics should be administered as soon as possible following injury after a wound culture has first been taken. The selection of antibiotics will vary from institution to institution with the experience of what organisms and what sensitivities are found in open fractures being used as a guide to antibiotic selection. Antibiotics that seem effective based on our experience are a cephalosporin used alone, a synthetic penicillin given with an aminoglycoside, and a cephalosporin given with an aminoglycoside.

The term prophylactic antibiotics is not appropriate since open fracture wounds are contaminated, and surgeons are in fact treating by giving antibiotics. Based on our data the use of antibiotics in the management of open fractures is unequivocally indicated.

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Scoliosis Screening

SCHOOL SCREENING PROGRAMS for detection of adolescent scoliosis have been endorsed by the Scoliosis Research Society and the American Academy of Orthopaedic Surgery. Many such programs have been implemented across the nation. The primary screening program is done in the school. The forward bend test is a reasonably discriminating method of detecting asymmetry of the back suggesting scoliosis. The technique is easily taught and with a minimum of experience the nurse examiner will become very proficient. This becomes an efficient program requiring physician participation only at the secondary screening level. Most programs in primary screening detect about 10 percent of children as having some back asymmetry.

At the secondary screening centers, single standing anteroposterior roentgenograms of the spine are taken for permanent record of the curvature and appropriate measurements of curves are made. False positive findings on primary screening occur in about 2 percent of cases. Of the remaining 8 percent, most of the students receive continued observation and are referred to physicians in the community. About 1 percent are referred for specific treatment, usually bracing. The goal of screening programs is to

identify early those youngsters who have scoliosis and through judicious treatment avoid the need for surgical operation.

Concerns over radiation exposure are important. It has been determined that a single screening radiograph results in an averaged absorbed dose of 173 millirads. Environmental exposure is approximately 100 millirads per year. Gonadal doses were approximately 21 millrads for males and 104 millirads for females. Although these doses are small, continued concern about long-term effects of low dose radiation remain. These effects are at present unknown. Studies are underway to correlate radiographically identified curves with topographic photography methods; that is, moire photography. Early results suggest this to be a sensitive screening technique and may eventually eliminate the need for most early x-ray studies.

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EDITORIALS

Welcome WSMA

BY ACTION of the Washington State Medical Association's House of Delegates the members of the Association will receive THE WESTERN JOURNAL OF MEDICINE as a benefit of their membership beginning with this issue. The editors welcome the nearly 5,000 new readers in Washington state to the growing *WJM* family. The *WJM* now serves as the official journal of the Idaho, Nevada, California and Washington medical associations, and as such it is truly a unique regional journal. This uniqueness, and growing strength, lies in the genuine roots the journal is establishing in state medical associations in the West.

The *WJM* seeks to be a truly useful journal for its readers, the greatest number of whom are practitioners. It seeks to offer a variety of fare which also will include something of interest for students, academicians, researchers and even political leaders of our profession—of whom there are many among its readers. It seeks to reflect the vitality and achievements in science, education and practice that are hallmarks of medicine in the West, and to give these a stronger presence in the medical literature. The editors, the editorial board and many others are dedicated to making this journal a regional instrument of physician education and continuing education in the West, and also an increasingly distinguished journal on the national scene.

The Washington State Edition will contain an innovation. For WSMA readers only there will be an insert prepared by the WSMA staff under the direction of the Special Editor for Washington. This insert will contain material of special interest to WSMA members and will serve as an important additional means of communication between WSMA and its membership.

We welcome WSMA. We look forward to a long and productive association which should be of great benefit to all concerned.

—MSMW

Allergic Bronchopulmonary Aspergillosis

AN IMPORTANT ARTICLE by Novey and Wells in this issue focuses on the increasing emergence of the disease allergic bronchopulmonary aspergillosis (ABPA). Described in England 26 years ago[1] and first reported in the United States 10 years ago,[2] an increasing number of cases is being identified throughout the United States. The study of Novey and Wells shows that a concentrated search for cases will result in recognition of previously unidentified cases. Therefore, a phase of awareness and recognition of the disease state has been achieved by alert investigators at some institutions and in practice. There are multiple curious and interesting facets of ABPA to be mentioned in this editorial. One of these is that some institutions with large clinical services have not yet identified cases of ABPA. In a recent discussion of the disease, a comment was overheard: "Oh, that is just one of those rare University-type diseases." The study by Novey and Wells clearly shows that ABPA is not rare and constitutes a significant medical problem in California. It must be emphasized that ABPA is not benign.

Early recognition is difficult because of a lack of criteria for specific diagnosis and those serologic tests most appropriate may only be available in specialized centers. However, early recognition appears important because of the potentiality for progression of ABPA to serious irreversible lung destruction. The late stage pulmonary involvement includes both the curious central bronchiectasis and pulmonary fibrosis with irreversible end-stage lung disease. The most important factor in diagnosis is suspicion of the possibility of the disease. Early cases of ABPA often will not have all of the characteristic clinical and laboratory findings of pulmonary infiltrates, pronounced peripheral eosinophilia, sharply elevated total serum IgE and

bronchiectasis. In patients with early ABPA, x-ray studies of the chest may show no abnormalities and asthma may be extremely mild, requiring only occasional bronchodilator therapy. It is our opinion that the possibility of ABPA must be considered in every asthmatic person, and the presence of ABPA can likely be excluded by showing the absence of immediate skin reactivity to aspergillus antigen. A positive skin test should lead to further investigation including a total serum IgE determination and search for precipitating antibodies against aspergillus antigen. It may be suggested at this time that reasonable, if not final, serologic diagnostic aids are and will be increasingly available. One of these diagnostic aids is the measurement of total serum IgE and IgG antibodies against Aspergillus fumigatus antigen.[3]

Although multiple therapies for ABPA have been attempted, prednisone therapy appears to be the treatment of choice. This results in clearing of lesions shown on x-ray studies of the chest and disappearance of clinical symptomatology. The duration of therapy required is uncertain and is under study. In certain patients, after prednisone dosage has been tapered and discontinued, there will be exacerbations of ABPA. In other patients in our study, therapy with steroids has been discontinued for prolonged periods without exacerbations. Consequently, commitment to permanent administration of steroids as a prevention of exacerbations does not seem appropriate in all patients.

The identification of the disease in the young population described by Novey and Wells is of importance. One of the questions about ABPA is what happens to patients who have not been diagnosed with ABPA which occurs in their youth. We have recently learned of a clearly diagnosed case of ABPA in which the first episode of pulmonary infiltrates with pronounced eosinophilia was documented 36 years previously. The patient now has end-stage fibrotic lung disease. It is to prevent this type of problem that ABPA must be identified early.

Some of the many curiosities and questions about ABPA that remain unanswered are as follows: The spores of the genus Aspergillus, a common saprophytic fungus, are a common aeroallergen; why does ABPA develop only in certain asthmatic persons? No defect in lymphocyte reactivity, polymorphonuclear function or monocytic function has been shown in these patients. What characteristics of A. fumigatus lead to this organism being so significant in causing ABPA, aspergillomas and disseminated aspergillosis in immunosuppressed patients? The organism is also incriminated as the cause of abortions in sheep and cattle through unknown mechanisms. The elevation in total serum IgE which occurs in patients with ABPA is unexplained. This elevation in total serum IgE may be dramatic, reaching 70,000 ng per ml in some patients (the laboratory normal value is approximately 100 ng per ml). It has been shown that all of this IgE is not IgE antibody directed against antigens of A. fumigatus.[4] The elevated serum IgE declines dramatically with prednisone therapy in patients with ABPA but the mechanism of action of predisone which results in clinical improvement of ABPA and the decline in total serum IgE is not clearly explained.

The immunologic mechanisms of the production of the pulmonary infiltrates, the central bronchiectasis and progressive fibrosis, are unclear. The organisms colonize the airways and antigens are undoubtedly released in the airways. The reaction of IgE antibodies against aspergillus antigens with the antigens present in the airways likely is important and mediators released from mast cells may permit passage of antigens through the bronchial epithelium. The IgG precipitating antibodies may produce an antigen-antibody complex reaction within pulmonary tissue, perhaps aided by the IgE mediated absorption of aspergillus antigen. The role of lymphocytes remains uncertain. Lymphocyte transformation occurs when lymphocytes in whole blood from patients with ABPA are stimulated by aspergillus antigen. Separated lymphocytes from some patients with ABPA do not respond to aspergillus antigen by lymphocyte transformation. Lymphocyte mediated damage has not been clearly shown or excluded.

Based on the article by Novey and Wells, it appears that different disease patterns of ABPA may appear seasonally, geographically and in relation to environmental exposure. Novey and Wells have identified ABPA in farm areas, suggesting environmental exposure in some patients and a prevalence for occurrence in the fall and winter months in California. In Chicago, we have identified a population in an urban area with little correlation with any environmental exposure and a probable prevalence of exacerbations of ABPA from the spring through the fall. This season, of course, is a period when there is an absence of snow cover in the Chicago environment and a

higher concentration of mold spores in the environment.

A most interesting possibility is raised by the Novey and Wells paper. Having identified ABPA as an important disease in California, it would be of interest if Dr. Novey was informed of how many further cases of ABPA were identified in the western states by the thousands of physicians who have read THE WESTERN JOURNAL OF MEDICINE and his report.

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Of Cults and Armageddon

THE RECENT gruesome events at Jonestown in Guyana remind us how little we understand about some aspects of human nature and human behavior. How more than 900 persons of all ages could engage in a planned, even rehearsed, ritual of murder and suicide defies comprehension in our present state of knowledge. As far as is known such an occurrence on such a scale is unprecedented in modern times. The awful thought arises that what has happened once can happen again, perhaps on an even larger scale, unless somehow we can gain a better understanding of this human aberration, and find better means of detecting it in an early stage and instituting effective prevention.

It is not really known whether there is some inborn weakness or defect which may make some persons susceptible and others not, whether there is something about a person's life experience or whether there is a form of psychological contagion which in a sense might infect persons. In some individual instances of murder and suicide insanity clearly plays a role, but not in all. There are instances in which both killing and suicide are rational acts—in self-defense or to avoid further suffering that is simply unbearable, for example. But neither individual insanity in so many persons at one time and in one place, or murder and suicide as rational acts, seem adequate to explain the horror of Jonestown. It seems that there must have been some element of contagious aberration which so affected more than 900 persons that they saw this evidently planned and to us unbelievable ritual of murder and suicide as, for them, a rational and presumably necessary act.

In this context one cannot help but think of the murderous atrocities perpetrated against the Jewish people in Hitler's Germany and the ultimate apparent suicide of the leader of the Nazi cult. Germany and the German people had seemed to be among the most sane and rational of peoples and yet they were somehow swept along by a charismatic and irrational leader who imposed his murderous irrationality upon that apparently most civilized nation. One cringes at the thought of what might have happened had that leader, who by this time was obviously insane, been in possession of the power to make his suicide global by pressing a button that would have released a holocaust of worldwide nuclear destruction. In such a circumstance, which we understand is technically possible today, Armageddon could be a reality.

Cults tend to form around charismatic leaders and charismatic leaders are often somehow not like other people. There is an infectiousness in their leadership that spreads among their followers and gives them power which can extend to life and death for their followers and for others. Perhaps the Jonestown experience is telling us something. It could be a warning that unless we find ways to understand the murderous and suicidal aberrations that can occur in charismatic leaders and their cults, find better means for their early diagnosis, and discover how to institute timely and effective prevention or countermeasures, Armageddon might just happen as a result of this poorly understood human aberration in persons in positions of great power. It would seem none too soon to begin the process of more certain prevention of this unthinkable but nevertheless quite possible circumstance.

—MSMW

Intussusception

THIS ISSUE of the WESTERN JOURNAL contains a Specialty Conference on the important topic of intussusception, to which this editorial will refer.

There will be general agreement today that a barium enema study is the conclusive diagnostic test when intussusception is suspected and that it should be undertaken in the expectation of apply-

ing it therapeutically if the diagnosis is confirmed. One would assume, although this is not mentioned in the conference, that in each of the patients a nasogastric tube was in place and intravenous fluid was running when the examination and treatment were undertaken. As indicated by cases 2, 3 and 4, the advantages of attempted reduction by hydrostatic pressure are not only the avoidance of operation in some 75 percent of the cases but a reduction of the intussusception to the right side of the colon or the cecum in virtually all of the rest (in fact, in 10 percent of those operated upon after "unsuccessful" reduction, the operation discloses that complete reduction had been achieved). It is not indicated that the barium enema reduction was conducted by a surgeon or with the surgeon present and the operating room formerly alerted to prepare for the operation. To undertake barium enema reduction in the office or even in the hospital without the participation of the surgeon who will do the operation, if one is required, invites unnecessary delay; it perhaps is not unlike having a radiologist manipulating fractures under a fluoroscope calling in an orthopedic surgeon only if open reduction is required.

One might be permitted some astonishment about Dr. Nyhan's description of mucus in the vomitus as if this were in some way related to the mucus in the currant-jelly stool. As we have shown experimentally, the epithelial cells of the intussusceptum are quickly converted into goblet cells swollen with mucus, the source of the jelly. It is not known to me whether it has been shown that in children with intussusception or any other type of acute intestinal obstruction, large amounts of mucus develop in the upper gastrointestinal tract. I have certainly not recognized such mucus production.

The concern about the reduction of an anatomical leading point lesion expressed in the conference by a member of the audience is, of course, a common one. One would agree that it is precisely those intussusceptions with polyps, enterogenous cysts and Meckel diverticula which are least likely to be successfully reduced by barium enema, and, in any case, these are not lesions which are, in themselves, as inherently dangerous as let us say a carcinoma causing intussusception of the colon in an adult.

It is difficult to escape the conviction that a very large proportion of intussusceptions are due to enlargement of the lymphoid patches in the terminal ileum, probably in association with viral diseases, although as the discussion indicates results of several studies are only strongly suggestive. It is noteworthy that many of the other conditions associated with intussusception involve hemorrhagic lesions of the mucosa—Henoch-Schönlein purpura, trauma, leukemia, chemotherapy.

No comment was made in the conference as to how late in the course of the disease it was still reasonable to undertake barium enema reduction, other than to state that the yield decreased progressively. Since patients have nasogastric tubes in place, are receiving fluids intravenously and are receiving antibiotics (always administered to any patient suspected of having potentially ischemic bowel), little is lost and much is gained by attempting barium enema reduction in all patients with intussusception. Some intussusceptions after several days are nonstrangulating and can be completely reduced and, in most of the others, the intussusception will be reduced to the right colon permitting a right lower quadrant exploration instead of a general laparotomy.

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The Increasing Use of Emergency Services: Why Has It Occurred? Is It a Problem?

THE ANNUAL NUMBER of emergency room (ER) visits in this country has risen from 18 million in 1958, to 44 million in 1968, and 77 million in 1977.[1-3] Although many of these visits are for emergency conditions, it is clear that as many as 70 percent to 85 percent are for nonurgent problems.[2-4] Blaisdell notes in the Trauma Rounds elsewhere in this issue of the journal that these trends were not caused by a recent epidemic of emergencies. Their roots are found in social and economic forces that must be understood in order to decide whether a problem exists that requires action.

As is the case with rising health care costs, the greater use of emergency services seems to be associated with factors related to both the demand

for and supply of medical care. Beginning with demand, patients seem to value the convenience of 24-hour access available at ER's. This is especially important for those without a personal physician, for families on vacation, or for persons who have recently moved. The decreasing availability of personal physicians, the increase in physician specialization, and the wide range of services immediately available in an ER are other suggested reasons why patients choose an ER as an alternative to a physician's office for nonurgent care. It is ironic that physicians are perceived as being less accessible at a time when the ratio of physicians to population is rising rapidly. Another demand factor, listed by Blaisdell, is widespread insurance coverage for emergency care. It often results in lower out-of-pocket costs for ER treatment than when the same nonurgent condition is treated in other settings. All these factors serve to encourage patient demand for ER services for nonurgent conditions.

Hand-in-hand with the increased demand for emergency care, an increase in supply also encourages use of ER's. Acute care hospitals are finding ER's to be an attractive means of filling empty hospital beds. Blaisdell, Mangold[5] and others claim that many hospitals have advocated open-door ER policies to combat decreasing inpatient occupancy rates and to generate hospital revenues.[5] For example, in San Francisco, a city with a high ratio of beds per population (5.6 per thousand compared with 3.9 for the state of California) and a low hospital occupancy figure (60 percent compared with 66 percent for California and 75 percent for the entire United States),[6,7] ER availability has expanded dramatically. According to Blaisdell, 14 of the 18 San Francisco acute care hospitals now have 24-hour ER's staffed by full-time physicians, whereas 10 to 15 years ago there was only one.

A number of factors have created incentives to staff these ER's with full-time emergency care "specialists." The ruling in the Darling case held hospitals legally responsible for care delivered on their premises by the medical staff.[8] It stimulated many hospitals to shift their ER coverage patterns, as did a 1971 California ruling by Attorney General Younger that prohibited hospitals from employing physicians specifically to render emergency services.[5] Today, large numbers of ER's are staffed on a contract basis by firms of ER physicians. The American College of Emergency Physicians, founded in 1969, now has 9,600 members and is pressing for separate board certification as the 23rd medical specialty.

Many physicians, especially recent graduates who may desire to remain in metropolitan areas with high concentrations of physicians, find ER work attractive. Financial advantages and predictability of hours on duty were the two main reasons for preferring emergency practice, according to a survey of physicians engaged in emergency care in Connecticut.[9] The reluctance of personal physicians to be on call outside regular office hours also encourages ER use, sometimes explicitly. This policy was forcibly argued recently by Egerton in *Medical Economics*. The author, a general practitioner, claimed that ER care was of higher quality than his own off-hours coverage and prophesied that the unrewarding anachronism of being on call would soon go the way of house calls. After all, he reasoned:

> Most of the problems that patients phone about can safely wait for normal office hours. The patient with a true emergency can't usually be helped over the phone, and there is some evidence that when a patient delays calling an ambulance to speak to his doctor, the results can be harmful. The on-call detail is also a considerable inconvenience and irritation to the doctor's family, possibly having adverse effects on his health as well. Who knows how many MD marriages have floundered on rocks such as these? And, finally, being on call can be financially unrewarding.[10]

Given the excellent record of well-staffed ER's in caring for real emergencies and the convenience they offer for routine problems, one might conclude, as did a recent article, "Perhaps we should stop asking why people come to an emergency department and instead ask why anyone gets his care anywhere else."[11]

There are at least two powerful arguments against ER use for routine care. The first is that the episodic nature and lack of systematic follow-up of *routine* problems seen in ER settings does not result in good quality care. At least some data support this argument. Studies by Brook at the ER's of Baltimore City Hospital and Johns Hopkins Hospital show that patient care was adequate for only about 25 percent of patients with nonurgent gastrointestinal symptoms. In general, diagnostic care was rated higher than formulation of management plans or patient outcomes.[12,13] For conditions such as hypertension, diabetes mellitus, gastrointestinal symptoms, behavioral problems, chronic depression, and others where long-term management and attention to patient compliance are essential for optimal care,

routine episodic ER care may be of poorer quality than continuing care by a personal physician.

The second argument is economic. ER care for nonurgent conditions is expensive. A recent survey of five San Francisco Bay Area hospital ER's ascertained charges for a patient with a sore throat who would be evaluated with a routine throat culture and a complete blood count. Charges ranged from $63 to $99 (Judy Schwartz, Health Policy Program Intern, unpublished data). These high charges may be necessary to cover ER expenses, but they clearly represent an inefficient and costly use of medical resources. Even if third-party insurance covers most ER bills, the consumer eventually ends up paying for the high cost of ER care through higher premiums and taxes.

The problem is how to improve the appropriateness of ER care. A range of remedies is apparent, none of which is without major drawbacks. The demand for ER services could be decreased by having patients share in the costs of care through deductibles or copayments. Such deterrents, however, are most effective for the poor, who are the group tending to be in greatest need of health care. Denial of payment for nonurgent ER care by third-party carriers might deter inappropriate use, but it would impose conflicting loyalties on physicians and hospitals and introduce another cumbersome claims review process.

Solutions addressed to the supply side could improve the accessibility of personal physicians. Reports in the medical literature suggest a reduction in ER use concomitant with the introduction of group practice.[14,15] However, without some fiscal or organizational incentives to provide comprehensive coverage, it is doubtful that this will occur. Recent attempts to increase the proportion of physicians in primary care practice could conceivably increase accessibility during off-hours, although this would not happen if they follow the advice of Dr. Egerton. Such a solution would be a long-range one, given the time required to train physicians.

Another potential solution is to develop 24-hour walk-in facilities for lower cost, easy-access, nonurgent care. These could be established in hospitals with large ER volumes. The hospital could adjust charges for their major and minor emergency care, which could result in higher bills for those with real emergencies. Alternatively, widely scattered lower cost 24-hour facilities could be organized to function as walk-in clinics, a solution adopted by many large group practices and health maintenance organizations. That a market exists for these facilities is attested by the development of free-standing emergency rooms that provide services completely independent of a hospital. These "ER's" are found in shopping centers in some Eastern states and are beginning to appear in the West. These solutions, however, would pose a direct threat to practicing physicians, might further increase patient demand for ER-type services and would almost certainly exacerbate the problem of the rising costs of medical care.[16] In the interim, perhaps ER's should be asked to recognize their responsibility for the follow-up of patients presenting for episodic care of nonurgent problems.[17]

It seems that the complexity of the problem of increasing ER use is more apparent than its solution. What is clear is that the prevention and treatment of real emergencies must continue to receive the kind of attention described in the Trauma Rounds, while we also begin to address the intricate problem of inappropriate use of ER's.

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CASE REPORTS

Refer to: Smith MS: Left upper quadrant presentation of Fitz-Hugh—Curtis syndrome in an adolescent. West J Med 130:70-72, Jan 1979

Left Upper Quadrant Presentation of Fitz-Hugh—Curtis Syndrome in an Adolescent

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THE FITZ-HUGH—CURTIS SYNDROME, gonococcal peritonitis of the upper abdomen, has rarely been described in adolescents.[1-3] Although left upper quadrant presentation has been noted in the Spanish and French literature,[4,5] emphasis in the English language literature has been on right upper quadrant signs and symptoms in association with gonococcal pelvic infection.[1,2,6-13] This case report describes the case of an adolescent girl with Fitz-Hugh—Curtis syndrome presenting with left upper quadrant pain radiating to the shoulder and normal findings on pelvic examination.

Report of a Case

A 16-year-old girl was evaluated for low back pain. Results of a physical examination (including pelvic examination) were entirely within normal limits. Analysis and culture of urine, Papanicolaou smear and endocervical culture for gonorrhea were negative. A presumptive diagnosis of low back strain was made and the symptoms resolved promptly with heat and salicylate therapy.

One month later she presented with a five day history of dull left upper quadrant pain. Deep inspiration, cough and lying supine or on her left side increased the pain. Truncal movement or palpation of the left upper quadrant elicited sharp pain in the left neck and shoulder. A review of systems was noncontributory and there had been no recent illness or trauma. She had menstruated normally three weeks before the onset of the abdominal pain. Pertinent physical findings were limited entirely to the left upper quadrant which was exquisitely tender beneath the lower costal margin in the anterior axillary line. Palpation produced radiating pain into the left shoulder and neck. A pelvic examination was not done at this time. The following laboratory studies gave values within normal limits: a complete blood count, erythrocyte sedimentation rate, analysis and culture of urine, sickle cell screen, amylase, serum glutamic oxaloacetic transaminase, blood urea nitrogen, glucose, Mono spot test and electrolytes. Findings on radiographs of the chest and abdomen, a technetium liver-spleen scan, abdominal and pelvic ultrasonography and an oral cholecystogram were all within normal limits. Over a period of 24 hours the pain decreased to a pronounced degree and a tentative diagnosis of diaphragmatic irritation, possibly related to muscular strain, was made.

During the next week the left upper quadrant pain was intermittent, dull and exacerbated by activity. A pelvic examination two weeks after onset of symptoms gave unremarkable findings except for a scant vaginal discharge which on wet mount showed six to eight epithelial cells and eight to ten leukocytes per high power field. Results of a repeat complete blood count and erythrocyte sedimentation rate were normal. An endocervical culture was negative for gonorrhea.

Eighteen days after onset the pain resolved in the left upper quadrant and shifted to the right upper quadrant, localizing in the midclavicular line subcostally. Findings on repeated physical examinations over the next ten days were unremarkable except for gradually decreasing tenderness in the right upper quadrant. There was no friction rub. One month after the onset of symptoms dull pain persisted and results of a pelvic examination again were within normal limits except for scant white vaginal discharge with ten white cells per high power field. An endocervical culture was positive for Neisseria gonorrhoeae.

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The diagnosis of Fitz-Hugh—Curtis syndrome was made and the patient's condition responded rapidly to 4.8 million units of procaine penicillin given intramuscularly with 1 gram of probenecid given orally. She was continued on a regimen of ampicillin, 500 mg given orally every six hours for ten days. Two weeks after the initiation of therapy physical examination showed no abnormalities and an endocervical culture was negative for gonorrhea.

Discussion

Carlos Stajano first described the syndrome of upper abdominal peritonitis associated with antecedent or concurrent pelvic gonorrhea in 1920.[4] In 1930 Arthur Curtis described "violin-string" adhesions between the surface of the liver and the anterior abdominal wall in patients in whom there was evidence of previous salpingitis.[6] In 1934 Thomas Fitz-Hugh assisted at an operation for presumed cholecystitis, found peritonitis of the anterior liver and adjacent peritoneal surface, and (remembering Curtis' report) identified gonococcal organisms in the peritoneal drainage but not from the cervix or urethra.[7] Fitz-Hugh subsequently found gonococcal organisms on pelvic examination in two other women with the same syndrome. All three of these patients recovered uneventfully with bed rest.

The most complete English language description of this syndrome was written in 1946 by Malcolm Stanley.[8] The typical patient frequently gives a positive history for genitourinary dysfunction (such as menorrhagia, discharge, dysuria) or vague lower abdominal pain occurring days to weeks preceding the onset of upper abdominal pain. Trauma may be a precipitating factor. The onset of symptoms is usually dramatic with excruciating sharp pain in the right upper quadrant, often referred to the shoulder or inside of the arm. The pain is usually increased with deep breathing, coughing, laughing and truncal movement. The pain may be on the left or bilaterally at onset and alternate from one side to the other. It may also present over the lateral rib margin or in the back. Hiccups, nausea, chills, fever, sweating and headache may be present. Occasionally a friction rub similar to "beautiful new snow creaking" is heard over the anterior costal margin.[7] There is usually no visceromegaly. Pelvic examination is frequently abnormal with obvious purulent discharge, but may be entirely normal with negative cultures. Transaminase values occasionally are mildly elevated and findings on an oral cholecystogram may be transiently abnormal. The erythrocyte sedimentation rate is frequently elevated.

The route of infection in the female has classically been considered to be an ascending one from the fallopian tubes to the paracolic gutters of the abdomen into the subphrenic spaces. A gliding effect of the liver during respiration may predispose to right sided involvement. Recent documentation of this syndrome in a male has raised the consideration of hematogenous or lymphatic spread.[11]

The differential diagnosis of right upper quadrant pain must include many entities (such as hepatitis, pyelonephritis, pancreatitis, appendicitis, peptic ulcer) but the most common misdiagnosis is cholecystitis and the literature is replete with examples of diagnosis made at laparotomy. With left-sided presentation the diagnosis may be even more obscure and splenic trauma or subphrenic abscess is often considered. A high index of suspicion must be maintained and repeated pelvic examination or laparoscopy may be necessary to confirm the diagnosis. Diagnostic yield might be augmented by the addition of rectal cultures (increasing positive gonorrhea cultures by 4 percent),[14] detection of eight or more Gram-negative diplococci in at least two polymorphonuclear leukocytes in vaginal discharge[15] or fluorescent antibody techniques (although not more sensitive than appropriately performed cultures).[16]

There is no consensus about treatment protocols in the literature. It appears that penicillin in route and dosage adequate for treatment of pelvic inflammatory disease[17] is appropriate. Acutely ill patients are probably best managed with an initial short course of intravenously administered penicillin followed by orally given ampicillin for ten days. Chronic symptoms unrelieved by intensive antibiotic therapy may dramatically subside after laparoscopic lysis of adhesions between the liver and abdominal wall.[13]

It is clear that gonococcal peritonitis of the upper abdomen occurs in adolescents and may present with either left or right upper quadrant signs and symptoms. With increased awareness of this syndrome and a high index of suspicion, many more cases of the Fitz-Hugh—Curtis syndrome in adolescents undoubtedly will be reported. Since asymptomatic urethral gonorrhea

has been reported in 40 percent of male contacts of females with gonorrhea,[18] aggressive tracing of contacts is indicated.

Summary

The Fitz-Hugh—Curtis syndrome, gonococcal peritonitis of the upper abdomen, usually presents with right upper quadrant pain and has rarely been reported in adolescents. The case of a 16-year-old girl in whom there was left upper quadrant pain and in whom initial findings on pelvic examination were normal is described.

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Peripheral Arterial Tumor Embolism by Malignant Tumor

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EMBOLIZATION OF A peripheral artery most commonly originates from the heart. Mural thrombus secondary to atrial fibrillation and myocardial infarction is the usual cause.[1,2] Rarer etiologies include atrial myxoma,[3] paradoxical embolism,[4,5] atherosclerosis,[6-9] subacute bacterial endocarditis,[10] fungal endocarditis,[11] release of prosthetic valve material,[12] idiopathic hypertrophic subaortic stenosis,[13] hyatid cyst,[14] echinococcal cyst,[15] ventricular aneurysms,[16] bullets,[17,18] mitral stenosis,[19,20] false aneurysms[21] and arterial malignancy.[22] This paper presents the 32nd reported case of tumor embolism and reviews its salient features.

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Report of a Case

A 53-year-old woman was admitted to Tucson Medical Center on January 21, 1977, with a 2½-hour history of severe pain, numbness and coldness of both legs. She had a history of organic heart disease and hypertension, but she was asymptomatic in those respects. She had been followed for the past year for a nonexpanding nodule in her right lung (Figure 1). On physical examination there were no pulses in the right groin or in distal arteries of either leg. A weak left femoral pulse was palpable.

An immediate retrograde bilateral aortoiliac and femoral embolectomy was carried out through common femoral arteriotomies and good flow was established in the extremities. The pathology report showed poorly differentiated carcinoma in the clot.

Tomography showed that the pulmonary mass was larger than was shown on routine x-ray of the chest. Examination of subsequent bronchoscopic washings showed possibility of malignancy. On February 9, 1977, an exploratory thoracotomy and right lower lobectomy were done. Postoperatively she was unresponsive because of cerebral vascular insult; she died February 12, 1977. On postmortem examination, an undifferentiated sarcoma of unknown cause was found with multiple tumor emboli to the right kidney, brain and liver.

The pulmonary lesion was a metastatic sarcoma (Figures 2, 3).

Discussion

Tumor is a rare cause of arterial embolization, and this is the ninth reported case of successful removal of a malignant tumor embolus (Table 1). Pathologic examination of the embolic specimen led to the correct diagnosis, illustrating the need for pathologic examination of all embolic material. All but one of the reported cases of tumor embolism were associated with lung malignancy, and the remaining one was due to aortic invasion of a pelvic osteogenic sarcoma with distal embolization.[22] The occurrence of tumor embolization during surgical operation for pulmonary cancer has been reported by others (Table 2), and several authors have suggested obtaining early venous control in resecting large lung tumors with known venous invasion.[6,12,29,30,32,36]

Figure 1.—Admission x-ray of chest showing lesion below right inferior pulmonary artery.

Summary

A rare case of peripheral arterial embolization by malignant tumor is reported and the literature

Figure 2.—Low-power view of tumor embolus in pulmonary vein.

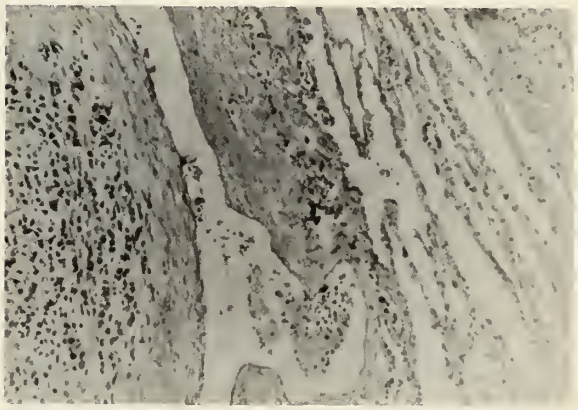

Figure 3.—High-power view showing tumor embolus in pulmonary vein.

TABLE 1.—*Systemic Tumor Embolism, Successful Removal*

Authors and Year of Publication	*Origin of Tumor Embolus*	*Obstructed Arteries*
Mital and associates, 1971[23]	Thyroid malignancy with pulmonary metastasis	Aortic bifurcation
DeBoer and Prillevits, 1969[24]	Undifferentiated lung carcinoma*	Femoral artery
Groth, 1940[25]	Tibial sarcoma with lung metastasis	Femoral artery
Blum, 1950[26]	Oat cell carcinoma of lung	Femoral artery
Firor and Pearson, 1967[27]	Squamous cell carcinoma of lung*	Aortic bifurcation
Soriano and associates, 1964[28]	Osteogenic sarcoma of fibula with lung metastasis	Femoral artery
MacMahon and associates, 1974[29]	Giant cell carcinoma of lung*	Distal aorta
	Undifferentiated carcinoma of lung*	Brachial artery
Personal observation	Metastatic sarcoma to lung*	Aortic bifurcation

*See Table 2.

is reviewed. Tumor emboli are usually pulmonary in origin, and they are commonly associated with surgical operation for pulmonary cancer. The value of pathologic and bacteriologic examination of all embolic material is emphasized.

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TABLE 2.—*Postthoracotomy Tumor Embolism*

Authors and Year of Publication	*Primary Tumor*	*Obstructed Arteries*
DeBoer and Prillevits, 1969[24]	Undifferentiated lung carcinoma	Femoral artery
Balas and associates, 1971[30]	Undifferentiated bronchial carcinoma	Aortic bifurcation
Probert, 1956[31]	Adrenocortical carcinoma with lung metastasis	Common carotid and innominate arteries
Eason, 1950[32]	Squamous cell carcinoma of lung	Cerebral arteries
Aylwin, 1951[6]	Bronchial carcinoma	Internal and axillary arteries
	Fibrosarcoma with lung metastasis	Aorta
Taber, 1961[33]	Pulmonary adenocarcinoma	Aortic bifurcation and multiple organ arteries
Christiansen and Morgan, 1965[34]	Undifferentiated lung carcinoma	Aortic bifurcation
Senderoff and Kirschner, 1962[35]	Thyroid carcinoma with lung metastasis	Femoral artery
Firor and Pearson, 1967[27]	Squamous cell carcinoma	Aortic bifurcation
MacMahon and associates, 1974[29]	Giant cell carcinoma of lung	Aortic bifurcation
	Undifferentiated carcinoma of lung	Brachial artery
Personal observation	Metastatic sarcoma to lung	Multiple organ arteries

TABLE 3.—*Systemic Tumor Embolism, Unsuccessful Removal or Diagnosed at Autopsy*

Authors and Year of Publication	*Origin of Tumor Embolus*	*Obstructed Arteries*
Rudusky, 1965, cited by DeBoer and Prillevits, 1969[24]	Maxillary chondrosarcoma with lung metastasis	Aorta and iliac artery
Loosemore and Whittick, 1951[37]	Synovioma of knee with lung metastasis	Axillary artery
Buckmaster, 1961[38]	Oat cell carcinoma of lung	Aortic bifurcation
Green and associates, 1974[39]	Colonic adenocarcinoma with lung metastasis	Multiple organ arteries
Till and Fairburn, 1947[22]	Oat cell carcinoma of lung	Femoral artery
Cera and associates, 1957[40]	Anaplastic bronchogenic carcinoma with atrial invasion	Coronary artery
Busse, 1903[41]	Chorioepithelioma metastatic to lung	Cerebral embolism
Storjohann, 1932[36]	Chorioepithelioma metastatic to lung	Cerebral embolism
Kaufmann, 1929, cited by Loosemore and Whittick[37]	Chorionic carcinoma with lung metastasis	Splenic and renal arteries
Miller and Jackson, 1954[42]	Pulmonary myxosarcoma	Splenic and cerebral arteries
Van Way and Lawler, 1969[43]	Osteogenic sarcoma involving the pelvis and distal aorta	Femoral arteries
Lisa and associates, 1941[44]	Squamous cell carcinoma of lung	Coronary artery
Hiraoka and associates, 1976[45]	Breast carcinoma metastatic to lung	Coronary artery
Haiby and Baitlon, 1965[46]	Bronchial adenoma	Multiple organ arteries
Mori, 1964, cited by Hiraoka and associates[45]	Lung cancer	Coronary artery

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Delayed Fat Embolism After Total Hip Arthroplasty

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THE SYNDROME of fat embolism is a serious clinical entity, the pathogenesis of which remains obscure. Although several reports have appeared describing the onset of the syndrome after joint replacement using methylmethacrylate, delayed onset of the syndrome has not been reported.[1] The present case report deals with a patient in whom this syndrome developed with rather late onset and recurrent features. The possible relationship to the use of methylmethacrylate will be discussed.

Report of a Case

A 64-year-old previously healthy man was initially seen because of increasing pain in the right hip. Vital signs were normal with the exception of an irregular pulse. There were bilateral rhonchi and wheezes; four to eight extrasystoles per minute were noted. An electrocardiogram showed unifocal premature ventricular contractions (PVC) and complete left bundle branch block. Results of complete blood count, analysis of urine and SMA-12 were normal. An x-ray film of the hips showed severe degenerative joint disease involving the right hip. The preoperative roentgenogram of the chest is shown in Figure 1.

A total hip arthroplasty was done on February 18, 1977, using an Aufranc-Turner prosthesis. The prosthesis was held in place with methylmethacrylate cement. The duration of the surgical operation was 110 minutes. The patient's vital signs were stable throughout the procedure. His urine output remained excellent during operation, exceeding 100 ml per hour, and the total blood loss was estimated at 1,200 ml. He was given 3,000 ml of lactated Ringer's solution and 1,000 ml of whole blood during the procedure. Continuous electrocardiographic monitoring showed rare PVC. Recovery in the immediate postoperative period was uneventful and the patient was transferred back to the ward in excellent condition. Postoperative treatment consisted of administration of cephalothin sodium, 1 gram given every four hours; heparin sodium, 2,000 units given intravenously every six hours, and morphine sulphate, given as needed for pain.

On the morning following operation the patient was resting comfortably. His temperature was 38°C (100.4°F) and other vital signs were normal. Total output was 3,130 ml (2,920 ml as urine and 210 ml from wound drainage). The hemoglobin and hematocrit values were stable at 13.3 grams per dl and 38.7 percent, respectively. Findings on an electrocardiogram (ECG) remained unchanged.

Thirty-six hours postoperatively the patient's temperature rose abruptly to 39.2°C (102.5°F), his respiratory rate was 36 breaths per minute and pulse was 120 beats per minute. He was confused, restless, disoriented, and incoherent. Diffuse rales were heard in both lungs and a petechial rash in the axillary and hypogastric regions de-

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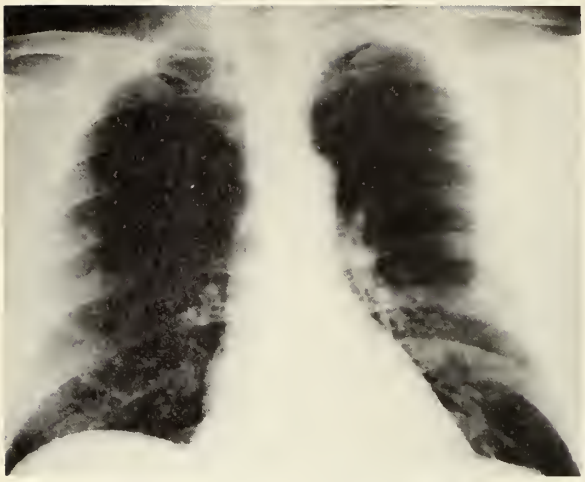

Figure 1.—Posterior-anterior roentgenogram of the chest done before operation.

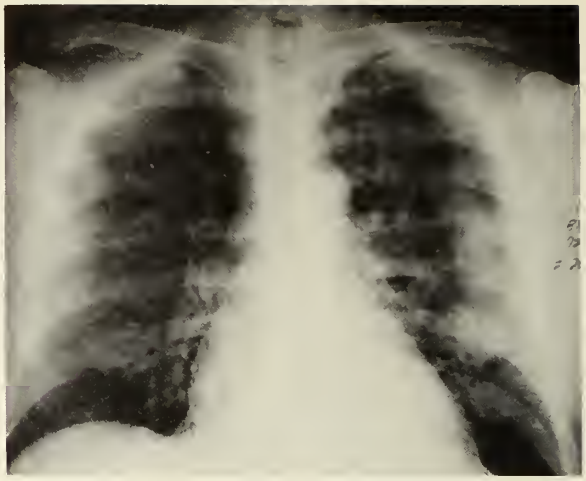

Figure 2.—Anterior-posterior roentgenogram of the chest done 36 hours after operation. Bilaterial patchy alveolar infiltrates are shown.

veloped. The leukocyte count was 9,000 per cu mm with a normal differential count. The hemoglobin value was 12.7 grams per dl and the hematocrit reading was 36.8 percent. A roentgenogram of the chest is shown in Figure 2. The ECG findings were unchanged. Cultures of blood, urine and sputum were obtained. Administration of cephalothin sodium was continued and the following therapy was added: supplemental oxygen; gentamicin sulphate, 80 mg given intramuscularly every eight hours; heparin sodium, 5,000 units given intravenously every four hours, and methylprednisolone sodium succinate, 60 mg given intravenously every six hours. While the patient was breathing oxygen at 4 liters per minute through a nasal cannula, arterial oxygen tension (Pa_{O_2}) was 63 mm of mercury, arterial carbon dioxide tension (Pa_{CO_2}) was 33 mm of mercury and pH was 7.46. Sputum and urine were positive for fat globules on sudan stain. Serum electrolyte, amylase, lipase, blood urea nitrogen (BUN) and creatinine values were normal.

Eighteen hours later the patient's temperature was 36.9°C (98.4°F) and mental status was normal. Forty-eight hours after the fever had developed the antibiotics were stopped. Supplemental oxygen administration was discontinued and blood gas values on room air showed a Pa_{O_2} of 61 mm of mercury, Pa_{CO_2} of 28 mm of mercury and pH of 7.41. The dosage of methylprednisolone sodium succinate was decreased over the subsequent 48 hours and discontinued 96 hours after having been started. Heparin administration was continued. Twenty-four hours later shortness of breath, tachypnea, chest tightness, low grade fever and recurrent petechial rash developed in the patient. Increasing fine rales were heard throughout the entire lung fields. The ECG findings were unchanged, but a roentgenogram of the chest showed an increase in infiltrates. Therapy with oxygen, methylprednisolone sodium succinate (60 mg given every six hours intravenously) and furosemide (40 mg given intravenously) was started. A repeat sputum specimen was positive for fat; a repeat urine specimen was not obtained. Twenty-four hours after institution of this regimen all symptoms had again abated and heparin administration was discontinued. Five days later methylprednisolone sodium succinate administration was stopped. At that point a roentgenogram of the chest showed no abnormalities (Figure 3) and the patient's subsequent course was uneventful.

Discussion

The classical features of the fat embolism syndrome were present in this patient. Fever, confusion, petechial rash, roentgenographic changes, and positive sputum and urine fat studies are most of the current criteria for establishing the diagnosis. However, this case also has some unusual features. The late onset of symptoms seems to be a rather unique occurrence in postoperative fat embolism syndrome.[2-6] The reason for this late onset was unclear in this patient.

Another interesting feature was the progression of symptoms in spite of heparin therapy. The patient was initially treated with low dose heparin given intravenously as a prophylactic regime

Figure 3.—Posterior-anterior roentgenogram of the chest done five days after operation. Resolution of infiltrates is shown.

against thrombosis. In spite of this the syndrome developed. This is consistent with present evidence and tends to reinforce the impression that heparin has no therapeutic effect on the fat embolism syndrome.[5]

A third interesting aspect of this case was the initial rapid response to corticosteroids and the subsequent return of symptoms after their withdrawal. Reinstitution of high dose steroid therapy was followed by rapid control of symptoms. We feel that this agent contributed to the control of this patient's symptoms. Reports are available showing the benefit of corticosteroids on the symptoms in selected groups of patients.[5,7] Other reports indicate that symptoms develop in patients already being given corticosteroids.[8] Studies in animals seem to indicate a lack of benefit from corticosteroids.[9] Although the answer to this problem is by no means clear, the evidence seems to indicate that use of corticosteroids in high doses in treating severe cases of the fat embolism syndrome is beneficial. This report seems to reinforce this view.

The exact relationship between the development of symptoms and the use of methylmethacrylate in this patient is unclear. In reviewing the events that preceded the onset of symptoms, no other obvious cause could be found. Methylmethacrylate has been implicated as the cause of clinical and pathologic findings similar to those seen with the fat embolism syndrome.[2-4] Previously reported cases and studies dealing with the toxicity of methylmethacrylate in animals have all emphasized the rapidity of the onset of symptoms after exposure.[1-4] The present case is most notable with regard to the late onset of symptoms after the use of methylmethacrylate. No previous report of late postoperative occurrence of symptoms could be found.

Absence of specific diagnostic and clinical measures for the diagnosis of the fat embolism syndrome requires a high index of suspicion by physicians who participate in the care of patients at risk for such complications. Patients in whom total hip arthroplasty has been done involving the use of methylmethacrylate cement should be considered at risk for the fat embolism syndrome to develop. In reported cases the syndrome seems to have developed early in the postoperative period. The present report emphasizes the possibility of late onset of the fat embolism syndrome in these patients.

Summary

The occurrence of the fat embolism syndrome in the early postoperative period following total hip arthroplasty has previously been reported. This communication describes the case of a patient in whom this syndrome occurred late in the postoperative course.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Prophylaxis of Tourists' Diarrhea

TO THE EDITOR: A group of tourists (mostly medical doctors and their wives) visited Egypt for nine days, stopping at Cairo, Luxor and Aswan. Because of a recent article on prophylaxis of tourists' diarrhea in the *New England Journal of Medicine*,[1] many of them took doxycycline (Vibramycin) 100 mg a day. Table 1 shows the results.

The woman who did develop diarrhea on a regimen of doxycycline had it mildly for half a day only. The others had it in varying degrees of severity lasting from one to ten days. For the purpose of classification only, cases severe enough to require medication were listed as diarrhea. There seemed to be no correlation between dietary precautions and illness. However, there were some cases of upper respiratory infections that were not prevented by the doxycycline. Although sunlight is said to cause reactions in patients receiving tetracycylines, the hot tropical sun of Egypt caused no problems.

In a family of four, only one member did not take the drug and she alone had diarrhea. It was a severe attack even though her only dietary indiscretion was the use of ice cubes. The doctors used a variety of medications as treatment for the diarrhea, especially diphenoxylate hydrochloride with atropine sulfate (Lomotil) and antibiotics. There seemed to be no correlation between type of therapy and duration or severity of the attack (see Table 2).

TABLE 1.—*Results of Doxycycline Therapy in 39 Tourists*

	Diarrhea	
	Yes	*No*
Taking doxycycline	1	13
Not taking doxycycline	17	8

TABLE 2.—*Results of Various Medications in Treating Diarrhea*

Medication	*Days of Illness*
Lomotil	7, 7, 8, 2, 10, 3, 5, 1
Lomotil and doxycycline ...	5, 2
Tetracycline	1
Paregoric and tetracycline ..	10
Cephalexin (Keflex)	4
No medication	1, 1
"Antispasmodics"	3

Egypt is a country of poor hygiene. Some 90 percent of the population at some time become infected with amoeba. The hotel facilities used were deluxe and a minimum of flies was observed during the trip. Those taking precautions drank bottled water imported from Italy. All other water used came from the Nile and it was impossible to get an honest assessment of what purification processes were used.

One has to conclude that doxycycline was an effective prophylactic for diarrhea in this group of tourists but apparently it is not effective as a treatment. One precaution should be mentioned: It must always be taken with food because it is quite irritating to the stomach. It is not known if other tetracyclines would have worked as well as the doxycycline.

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Scombroid Poisoning

TO THE EDITOR: I read with great personal interest the very complete article in the November 1978 issue of the WESTERN JOURNAL by Lerke, Werner, Taylor, et al on "Scombroid Poisoning: Report of an Outbreak" and felt that I perhaps might be able to answer some questions raised by the authors. As a former fisherman and wholesale fish distributor employee, and presently supported by my father, a commercial tuna, bonito, mackerel (alas, scombroid) fisherman from San Pedro, I feel I might be able to bridge the gap

between the physician-epidemiologists and the fish providers. In their discussion, the authors raise two important points: (1) that histamine is produced at high temperatures, hence the question of how the fish were cooled ("whether they were put on ice or in a refrigerator") is of prime interest in understanding the epidemiology, and (2) the observation that histamine levels vary tremendously within the same fish.

In considering the first point, I feel the authors were unclear on the differences in storage between tuna that is held for "fresh" and that which is frozen for canning. As pointed out in their article, the choicer fish are reserved for the fresh fish trade. These fish usually are larger and are never stored for longer than three to four days. They are usually the "first-brailled" fish or those fish first placed in the hatch. These fish have not had the same chance to decompose as long as the other fish killed in the catch. They are then treated initially in the same way as the brine fish; that is, they are rapidly cooled to 28 to 32°F (this usually takes 12 to 18 hours). Then, for the fish intended for canning, sacks of salt are added and the fish are frozen. However, with the fish held for fresh sale, the water without added salt is maintained at 32°F and the fish remain chilled but not frozen. Hence, I believe the impression the authors leave that "the rate of cooling must necessarily have been considerably slower" is not correct. Having spent my undergraduate summers off the coast of Southern California fishing for tuna commercially, I know that fishermen, because of the economic incentive that fresh tuna bring, make every effort to rapidly chill but not freeze the tuna because firmness and rich color are the main qualities sought by wholesalers and sashimi consumers.

The second point made in the article, the very uneven distribution of histamine in the spoilage of fresh tuna, prompts an observation. In the Japanese tradition, the "belly" portion of the tuna is preferred and, therefore, gourmets of sashimi may well be affected more often by scombroid poisoning.

I hope my comments add to the excellent discussion on a rare but interesting epidemiological, pathophysiological and public health problem.

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On Delineating Hospital Privileges

TO THE EDITOR: Time was when just being a good and conscientious physician was enough. We cared for our patients to the very best of our ability and everyone seemed satisfied. But nowadays that just does not suffice.

For example, this month at our community hospital staff meeting each physician was asked to fill out a sheet entitled "Delineation of Medical Privileges—Well Defined Category Approach."

In it we were asked to fit ourselves into category I, II, III or IV as to our ability to treat "organ systems or disease groups listed below." We were directed, in essence, to document for the hospital whether we considered ourselves first-class doctors or fourth-class doctors in the "privilege categories" related to disease entities ranging from allergy to rheumatology. Apparently, this information was to be on file in the administrator's office.

At last month's staff meeting we were handed a list (another paper to be filed in the front office) in which we were to check off a variety of procedures—spinal punctures, umbilical catherizations, circumcisions and so forth—that we were capable of doing, and that thereafter we would be allowed to do.

Month after month at staff meetings each committee and each department is asked, urged, required to spell out on paper its policies, to be entered in a policy book. And this policy book will be at every nursing station available for handy reference not only for the nursing staff, but for orderlies and nighttime cleanup crews, and conceivably for a plaintiff's attorney who may need a juicy bit of information.

If we have the temerity to ask why all this categorization and documentation is necessary we are told "Oh, it's required by the Joint Commission." If the mention of that august body is not enough, we are admonished "We have to take the hospital off the hook."

Unfortunately, most of us meekly comply, in the name of preserving our precious and sacred staff privileges.

Isn't it time that we practicing physicians awaken to the fact that each time we accept one more delineation of privileges or categorization of our capabilities, or that each time we etch one more policy in stone, we are actually painting ourselves into a tight little legal corner?

Isn't now the time to cry "enough"? Don't we

have the courage to call a halt to this regimentation? Shouldn't we dig in our heels and remind our hospital boards and the Joint Commission that we are private practicing physicians, not hospital hirelings? That we are individual contractors, owing our first and foremost obligation to our patients? That each one of us is dedicated to the proposition that through training and experience we must depend not upon a policy book, but upon our own good judgment as to how our patients will be cared for?

It is well and good for us to make every effort to "take the hospital off the hook." But in so doing let us not forfeit our right of decision making in matters of patient care.

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Intercostal Tube Drainage in Staphylococcal Pneumonia

TO THE EDITOR: In the Specialty Conference on staphylococcal pneumonia by Canty and associates in the September issue (West J Med 129: 201-209, Sep 1978), the discussion concerning the need for intercostal tube drainage in the treatment of staphylococcal pneumonia in children does not, I believe, reflect the current approach to the management of this condition.

The conference concludes by stating that intercostal tube drainage is "mandatory" in all cases of empyema complicating staphylococcal pneumonia. On the contrary, I believe that intercostal tube drainage now is indicated infrequently. Historically, it is true, tube drainage, open drainage and occasionally decortication were proposed. Since the early 1960's, probably as the result of new and effective antibiotic therapy, staphylococcal pneumonia with empyema has become less virulent in children. The pleura is a very effective barrier against the spread of infection, consequently the empyema will take care of itself provided the underlying lung is healthy and expanded. Excellent results, therefore, are obtainable by controlling the pulmonary infection alone by the use of appropriate antibiotics given in adequate doses over a suitable length of time.

The radiodensity characteristic of staphylococcal pneumonia with empyema has two components: one is pulmonary consolidation, the other is fluid. The fluid may be a very thick, shaggy fibrinoid exudate, or watery, or an admixture. Because it is often thick or loculated, or both, needle thoracentesis or tube drainage will yield, not uncommonly, only a small amount of fluid, even when an x-ray study of the chest is interpreted as showing a "large effusion." Intercostal tube drainage is ineffective in these instances and is not indicated.

Invasive procedures are necessary only in problem cases. Needle thoracentesis is indicated when it is desirable to obtain fluid for bacteriologic examination or when the diagnosis is in doubt. Intercostal tube drainage should be considered only in the patients with tension pneumothorax, mediastinal shift associated with considerable fluid, or in an extremely ill infant or a child who is not responding despite adequate antibiotic therapy. The patient presented by Daley in the conference fits into this group, and appropriately had tube thoracostomy.

As thoracic surgeons, we frequently are called upon to see patients with staphylococcal pneumonia with empyema, and it can be difficult to convince physicians and house staff alike that intercostal tube drainage is not indicated. Of course, the decision not to place a chest tube may be reversed by a changing clinical course, and careful follow-up by the surgeon while the patient is in hospital is imperative. The best estimate of a therapeutic response is the improvement of the patient. This usually precedes by many days any significant change in the appearance of x-ray studies of the chest. The adage to treat the patient and not the x-ray film is a good one to keep in mind in this condition.

This conservative approach to the treatment of staphylococcal pneumonia in children produces uniformly good results, spares most patients an unnecessary invasive procedure—thereby lessening their discomfort—and may even shorten the hospital stay.

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* * *

Dr. Canty Replies

TO THE EDITOR: I read with interest the letter by Dr. Bernard Tucker regarding our recent article about staphylococcal pneumonia. I appreciate his

thorough reading of the article and quite pertinent and cogent comments to which I will respond.

I would agree totally with Dr. Tucker in his feeling that not all staphylococcal empyemas according to his description warrant tube thoracostomy. The exquisite sensitivity of this organism to antibiotic therapy obviates the need for this in many cases. This is especially true for those empyemas which appear as small radiographic fluid collections blunting the costophrenic angle or resulting in blurring of the diaphragm on an upright film. The vast majority of these will respond to antibiotic therapy alone.

However, in those particular infants who are often seen late in their infective course, who are quite toxic and who have a significant empyema with an air fluid level, often the result of a ruptured pneumatocele, we do believe tube thoracostomy is indicated. This particular pattern is uniquely common with the staphylococcal organism in infants where frequently the "pneumonic" phase of the disease is quickly passed through in progression to frank empyema. This is not true in older children and adults. The proper placement of a chest tube by a skilled surgeon under optimal circumstances we feel is the conservative approach and not associated with discomfort. This will often rapidly improve a risky, if not life-threatening, clinical situation, and further, it may greatly shorten the hospital stay. The rapid response in these kinds of infants to tube drainage and antibiotics with virtually no additional morbidity supports this view. These principles also concur with Dr. Tucker's feeling about treating patients and not x-ray films, with which we wholeheartedly agree. I appreciate Dr. Tucker's comments and the opportunity to reply.

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Community Hospital Continuing Medical Education— A Missed Opportunity

TO THE EDITOR: Community hospital based Continuing Medical Education (CME) activities continue to be a sorely neglected portion of CME efforts. The benefits of such programs when well organized and implemented include: (1) problem-oriented learning, with its educational advantages related to direct physician involvement in local medical problems and personal knowledge of the patient, (2) the flexibility and adaptability of the local teaching programs to local needs, exceeding by far that of the usual "out-of-town" offering by a university medical center, (3) the enormous saving in time for physicians who may attend local CME meetings during their lunch hours as opposed to leaving their office for several days and (4) the substantial monetary savings to practicing physicians, not only by reducing their time away from office, but also by reducing expenses incurred from travel, food and lodging, and rising tuition fees.

Although these benefits are widely acknowledged, the overwhelming amount of educational time, money and energy continue to be channeled into the more traditional topic-oriented programs offered through and by most university medical centers, presented at their own institutions. The magnitude of this effort is amply illustrated by a three-month count in my own office: more than 90 circulars were received from all manner of medical institutions, advertising professional meetings in some portion of the state, nation or world. Most assuredly, these programs present useful information, but to the degree that they are prearranged topic-centered lectures, they are inferior to *problem-oriented* community hospital based CME programs for the actual delivery of *utilizable,* retained or recallable medical information.

In California, organized medicine has manifested some concern with these local programs through its CME inspecting teams which periodically survey community hospitals for category and accreditation. But the attention devoted by the California Medical Association (CMA) to local problems in CME goal definition, organization, resource availability and program implementation has been small indeed, with the result that the local programs commonly languish, appearing better on paper than they actually are. Both the CMA and the educational medical centers might be of great value to community centers in California by assuming more leadership in the discussion of projects such as the following:

- Arrange workshop meetings with local CME directors for reviews of community CME financing, needs determination and program implementation.
- Provide an organizational format which would permit the university medical educational center to receive from participating community hospitals requests for an informational program

based on a specific perceived need, tape a program designed to deal with this need (video taping of a didactic lecture) and return it to the community hospital for its use. Should the need prove to be common to several participating community hospitals, the tape might be kept on file for a limited time for further circulation.

- Continue to offer faculty lecturers upon request as is now widely done.

The availability of educational resources in the medical educational community on one hand, matched against the evident need for improvement in CME activities in the local medical practice community on the other, provides us with an opportunity for mutual reciprocal benefit, since the educational community could sell services while the private practice community could improve its CME programs by purchasing these services.

I submit that, to date, we have paid only lip service to community hospital based CME programs. However, with the increasing emphasis on continuing medical education, a reaffirmation of interest at all levels coupled with a concrete action plan for this type of physician education is appropriate, desirable and urgently needed.

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Cigarette Smoking and Drug Metabolism

ONE OF THE THINGS that we measure among many others in all these patients is smoking; we get a smoking history on everybody, and we look at the relationship of smoking to drug effects. . . . It turns out that smokers do apparently induce certain liver microsomal enzymes that metabolize drugs; and therefore in smokers certain drugs are metabolized more rapidly and their effect is less. We do measure efficacy on all these patients for all the drugs and we get a rate of ineffectiveness. This is simply where the physician taking care of the patient decided that the drug was ineffective. The ineffectiveness rate of propoxyphene (Darvon) is twice as high in heavy smokers as it is in nonsmokers. This goes along with metabolic data in the literature which show that the blood level of pentazocine (Talwin), a very closely similar drug, is very much lower in smokers than it is in nonsmokers. We believe that this result is probably valid and that it represents increased metabolism of this drug by people who smoke. We actually found a good half dozen drugs that affect smokers quite differently than nonsmokers, and this includes the benzodiazepines. We have rates of toxicity to diazepam (Valium), chlordiazepoxide (Librium) and phenobarbital according to smoking status, and nonsmokers have a rate of around 8 percent, heavy smokers 3 percent; for Librium, 10 percent versus 4 percent. This situation does not hold true, however, for phenobarbital; smoking does not appear to play a role in its clinical effect. But it is quite clear from these data that in smokers there is less of a clinical effect from Librium and Valium than in nonsmokers.

—HERSCHEL JICK, MD, *Boston*

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Trauma Rounds

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This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Allen RE, Teufel WL: Organization of emergency medical services (Trauma Rounds—San Francisco General Hospital). West J Med 130:83-89, Jan 1979

Organization of Emergency Medical Services

F. WILLIAM BLAISDELL, MD:* In the past ten years, organized medicine has been confronted with a remarkable phenomenon—the rapid proliferation of emergency medical services throughout the United States. Until 10 or 15 years ago, there was but one full-time emergency facility in San Francisco while at present 14 of the 18 hospitals in the city have 24-hour emergency rooms manned by full-time physicians.

This radical change has not been brought about by an epidemic of emergencies. Although there has been a trend toward more violence-related emergencies, the total number of emergencies in San Francisco has not changed appreciably over the past 10 to 15 years.

The reasons for this dramatic change appear to relate primarily to two factors. The first of these is a change in attitude by both patients and physicians; all seem to be moving toward the hospital as the basis for both inpatient and outpatient medical care. The reason for this, in turn, relates to the fact that physicians are working shorter hours and consequently may not be available to their private patients when the need for medical care (which is often crisis-related) develops. In addition, with a progressive increase in specialization in medicine, the patient's own physician, even if available, may not be capable of dealing effectively with his patient's particular problem. Most important, a well-equipped hospital is capable of providing a wide range of sophisticated diagnostic and therapeutic services.

The second major reason for the nationwide trend toward proliferation of emergency medical services relates to economic factors in our free enterprise society. Before the Medicaid and Medicare programs were instituted in 1966, a patient who presented to the hospital for crisis care was most commonly a nonpaying one or one who, when capable of paying for emergency care, frequently nonetheless did not. But with the advent of federal and state health insurance programs, most patients became eligible for third-party payment, the rising cost of emergency care could be passed on to a third-party payer while the patient himself remained only vaguely aware of the actual skyrocketing costs of these expensive services. Increased utilization of emergency rooms therefore permitted billing at premium rates for care of illnesses that were formerly managed much less expensively in doctors' offices and it became possible to hire emergency room physicians at salaries averaging $60,000 per year because of the

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premium rates charged for delivery of these "emergency" services. Furthermore, hospitals encouraged the use of emergency rooms for primary care because it generated greater utilization of their diagnostic services and promised to fill empty hospital beds. As a result of these forces and motivations, every hospital has been allowed to develop whatever services it wished without regard to whether such services were actually needed in its particular community.

But most recently, increased consumer awareness is developing regarding the implications of this trend, in terms of health care costs. The passage of the Cranston Act, the activities of the Department of Health, Education, and Welfare, and the development of Health Service Agencies have all pointed out loudly and clearly that this situation will not be tolerated by the public indefinitely. It seems evident that if the health profession is not capable of improving its organization, the consumer will institute measures to do so.

Our symposium today is designed to discuss some of the concepts being developed in relation to emergency medicine and to outline the benefits of organizing such services, including improved cost effectiveness.

I have asked Dr. Robert Allen to discuss prehospital aspects of the emergency medical care system.

ROBERT ALLEN, MD:* The basic philosophy regarding emergency medical care has changed drastically over the past several years. The idea that emergency medical care started and stopped in the emergency department of a hospital has given way to the much broader concept that emergency care should be extended out from the hospital to the ill and injured in the field.

This prehospital component of the emergency care system is theoretically as important as the hospital-based care if further major impact is to be made in improving survival rates and in decreasing disability secondary to emergency injuries and illnesses. Therefore, it is essential that the operational design of the emergency care system be such that orderly and logical functioning of the various components is ensured.

The increased nationwide interest in extending emergency medical care received its initial impetus from President Nixon when, in the State of the Union Message of January 20, 1972, he stated "I am directing the Department of Health, Education, and Welfare to develop new ways of organizing emergency medical services. . . . Today it often seems that our service programs are unresponsive to recipients' needs and wasteful of the taxpayer's money. A major reason is their extreme fragmentation."

As a result of this expressed interest by the President, directives were sent to the Department of Health, Education, and Welfare to develop a means for encouraging consolidation of emergency services. The concepts of regionalization and categorization of services were developed and their implementation made possible by Senator Alan Cranston who initiated legislation—the Cranston Act, Public Law 93-154—passed by Congress in 1973. However, recognition of the need for improved and advanced emergency medical care had germinated and was growing long before President Nixon took this initiative. During the Vietnam conflict, the rapid transport of victims from the front lines by helicopter to base hospitals which could provide comprehensive emergency services and definitive care—bypassing field hospitals—resulted in such a low mortality rate from serious injury that it has yet to be duplicated in civilian practice. In recent years, new techniques such as cardiopulmonary resuscitation and the technology of biotelemetry have been developed which have permitted skills in the resuscitation of critical emergency victims to be extended to the field. These new concepts were first applied to the emergency care system in Belfast, Ireland, by J. F. Pantridge and involved the prompt administration of advanced life-support techniques to heart attack victims at the site of cardiac arrest. As a result, since that time a major campaign has been mounted toward reducing prehospital deaths due to coronary artery disease.

Major considerations to be made in developing an emergency medical care system are those relating to the demography, geography and traditions of a particular region. The offices of Emergency Medical Services of the Department of Health, Education, and Welfare have made a continuous effort to standardize emergency care nationwide, an idea that is courageous and laudable. However, an emergency care system must assume responsibility for unique local needs of its citizens in addition to fulfilling fundamental criteria for delivery of quality emergency care. Any given system should also be cost effective and affordable. But before too much emphasis is placed on afforda-

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bility, it must be determined how much a human life is worth.

Problems encountered in relation to developing rural emergency medical care systems are quite different from those encountered in metropolitan areas. In rural areas, the primary problem relates to attempts at promptly entering the emergency care system and at shortening its response times. In contrast, in metropolitan areas where there is the potential for rapid entry into the emergency health care system, the primary problem is how to deliver prompt, definitive hospital care once a patient arrives in an emergency department. In the latter instance, categorization of hospital capability then becomes the key factor in developing quality health care delivery.

In 1972 San Francisco, through the city's Department of Health, upgraded its emergency medical care system primarily by instituting training programs for its personnel and by developing a sophisticated communications system. The triage pattern within the City and County of San Francisco had formerly been set by tradition; for the past 80 years, all patients who were seriously ill or injured were automatically taken to San Francisco General Hospital. But after all activities of the emergency care system in the prehospital phase were analyzed, it was found that 63 percent of this activity was trauma-related while the remainder consisted of treating miscellaneous lesser "emergencies." Traumatology training was therefore given priority. Each ambulance attendant was trained to the advanced life-support level and each ambulance driver to the basic life-support level. In addition, a system of first responders through the Fire Department was instituted to cut down on response times. To date, we do not as yet have adequate data to document the degree to which this new system actually has improved salvage rates and reduced morbidity over that of the old system. But we believe that the effectiveness of the health care system has been extended into the prehospital areas by this new system's approach. Training paramedic personnel, improved communications and transportation of victims with treatment initiated en route utilizing telemetry control from a physician in a base station have vastly improved the efficiency of our emergency medical care system.

DR. BLAISDELL: I would like to ask Dr. Donald Trunkey to comment about whether or not trauma centers are effective.

DONALD D. TRUNKEY, MD:* There are several factors that determine whether or not trauma centers are effective.

First, trauma centers are extremely costly; hence, there must be a demonstrated need for them. We recently published data in the *Journal of the American College of Emergency Physicians*[1] showing that California had need for somewhere between 12 and 16 trauma centers or trauma programs, based on the total number of emergency injuries treated annually and on geographical considerations. I believe Dr. Teufel will enlarge upon the issue of costs of trauma programs in his presentation.

The *second* factor concerns the actual provision or quality of emergency care. There is no question that over the past ten years there has been considerable improvement in techniques used to resuscitate trauma victims, particularly those used by paramedics in the field. Ideally, with the delivery of a patient to an emergency room, this resuscitation effort is continued and augmented. Resuscitation by itself will not guarantee salvage of the victim. This will be dependent on definitive care. But the problem is that of the 542 acute care hospitals in California, 419 have 24-hour emergency rooms. Most of these facilities are capable of initial resuscitation but they do not have prompt definitive care capability; that is, they are not able to provide such services as immediate operation for control of internal hemorrhage.

The public is very confused about the implications of this latter factor; that is, resuscitation capability versus definitive care capability. They simply do not know what is available based on what the hospital sign says. Fully equipped trauma centers can provide 24-hour definitive care by in-house staff while emergency rooms can provide resuscitation but may or may not be able to provide prompt, definitive care. Hospitals must provide specific capabilities and the public must be made aware of what they are.

My colleagues and I have been concerned about this discrepancy between resuscitation and definitive care capabilities. Consequently, in 1974 we reviewed an autopsy series in San Francisco County where victims of most injuries are transported to only one trauma center. The results of this study, which were also published in the *Journal of the American College of Emergency*

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Physicians,[2] showed that the presence or absence of prompt, definitive care capability was indeed a factor in determining ultimate outcome. In essence, it was shown that unnecessary or preventable deaths accounted for only 3 percent of all mortality in a hospital with 24-hour trauma capability, while in hospitals where services were not immediately available, this mortality rate could rise to as high as 66 percent.

However, this study could be criticized since it was confined to a single geographical area. But its results are nonetheless supported by similar studies done in Baltimore[3] and in the state of Texas.[4] Based on the results of our study and of these latter two in Baltimore and Texas, Dr. John West, a member of the American College of Surgeons' Committee on Trauma (Southern California Chapter), conducted a similar study comparing mortality in his county with that in San Francisco County.[5] Summarizing the results, an analysis of 100 consecutive trauma deaths in each county showed that most of the deaths in San Francisco County were due to neurological causes. Of its 15 nonneurological deaths, only one was considered possibly preventable. In contrast, in the Southern California county 31 of the total number of deaths were due to hemorrhage; of these, 21 were considered preventable in that the patients received operations late (if at all) and had relatively simple injuries such as ruptures of the spleen, lacerations of the liver and lacerations of the mesentery. We believe patients with these types of injuries should be salvageable more or less routinely by a sophisticated, well-organized system.

While this study supports the concept that trauma centers are effective, it does not address the problem of need for such centers. Actual need for trauma centers is arrived at only as a result of knowing the incidence of trauma within the various geographical regions that the center(s) would serve. We do think, however, that this last study does lend credence to the belief that the ability to administer definitive care promptly is the most important factor. This does not entail transporting trauma victims to the nearest hospital. In fact, with modern transportation and with the available expertise of paramedics, it is far better to transport victims to hospitals with 24-hour definitive care capability. I also feel strongly that it should be surgeons who set the guidelines for how many trauma centers or trauma programs are needed and that we should not abrogate this responsibility to other health care professionals or health planners who do not have the experience with treatment of trauma patients that we have.

DR. BLAISDELL: Dr. William Teufel has done an extensive study of emergency medical services and has made recommendations as to how trauma centers can be developed that meet the needs of the population, yet also are cost effective. Results of this study were published in the December 1977 issue of the *Journal of the American College of Emergency Physicians.*[1]

WILLIAM L. TEUFEL, MD:* I will review briefly some aspects of trauma center development that Dr. Donald D. Trunkey and I recently outlined in a paper presented at the University Association for Emergency Medicine's annual meeting in Kansas City, Missouri, in May 1977.

In recent years, national and state governments and organized medicine have attempted to define the optimal trauma center.[6,7] While they have developed some definitive guidelines, they have not adequately addressed three major factors, the consideration of which is essential for effective planning of trauma centers: realistic staffing patterns, costs associated with such staffing and criteria for determining the actual need for such trauma centers.

If one reviews the guidelines for an optimal trauma center as published by the American College of Surgeons' (ACS) Committee on Trauma and the Health Services Administration[6,8] and then applies recent salary figures (from a survey published in *Medical Economics,* April 1975), the yearly staffing costs for such trauma centers are easily calculated. One finds that the ACS optimal trauma center would cost $3,679,440 and that a center such as proposed by the Health Services Administration would cost $2,692,790.

Additionally, as extensive as these lists may appear, neither includes first and second surgical assistants who are often required for adequate operative intervention in relation to multiply injured trauma victims. Also, neither of these plans addresses the problem of backing up the initial trauma team once one patient enters the operating suite.

At present, only a few large university teaching hospitals actually approach these staffing patterns and they use residents as surrogates to maintain 24-hour coverage, with a corresponding reduction in staffing costs. It is obvious that without major

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TABLE 1.—*Community Hospital Trauma Program Physician Staffing Pattern*

In-House 24 hours a day	
Five Minute Availability	
Emergency physician	1
General surgeon	1
Anesthesiologist	1
Promptly On-Call 24 hours a day	
15 to 30 Minute Availability	
Orthopedist	1*
Neurosurgeon	1*
Internist	1
Radiologist	1

*Expected to function as first surgical assistant to general surgeon, if needed.

modifications, such trauma center staffing patterns are impossible for a community hospital to fulfill, since they have little or no house staff available.

In order to develop practical standards for an alternate "optimal" unit for a community hospital, we have arbitrarily designated the ACS optimal categorization as a "trauma center." Our proposal for a community hospital, designated a "trauma program," includes attainable staffing patterns with maintenance of quality medical care.

Community Hospital Trauma Program Staffing Pattern

In many of the suburban and rural areas of our country, a number of community hospitals without house staff provide care for trauma victims. These emergency departments are covered, to an ever increasing extent, by contracted groups of full-time emergency physicians with varying degrees of training. Many of these hospitals have some type of in-house anesthesia coverage but very few have either a surgeon or an operating room crew after daytime hours. However, most of such hospitals have on-call general surgeons, orthopedic surgeons, internists, radiologists and, to a lesser degree, neurosurgeons.

In our pattern for using such physician resources (Table 1), the in-house team consists of one general surgeon, one anesthesiologist and one emergency physician. We feel this is the minimum number of physicians needed to rapidly resuscitate a critically ill or injured trauma victim and to secure temporary operative control of hemorrhage. This proposal does provide critical in-house surgical coverage. We believe that many community hospitals are capable of meeting this in-house staffing pattern, even with limited manpower.

In addition, community hospital trauma programs must have physicians in the following surgical subspecialties on call within 30 minutes: thoracic surgery, urology, obstetrics and gynecology, ophthalmology, otolaryngology, and plastic surgery.

Prompt availablity of on-call physicians (Table 1) is crucial to the effective operation of the trauma program. The orthopedist, neurosurgeon, internist and radiologist are the four specialists most frequently called to support the general surgeon and his resuscitation team. The success of this plan is also based on the fact that the neurosurgeon or orthopedist will act as the first surgical assistant to the general surgeon when operative intervention must be immediate and when time does not permit contacting another surgeon. This role will be either new or uncomfortable for many practicing orthopedists and neurosurgeons. However, often a multiply injured trauma victim needs the combined services of a general surgeon, neurosurgeon and orthopedist, so the orthopedist and neurosurgeon would need to be present regardless.

Essential to this staffing pattern is a paid, part-time program director, appointed by the medical staff, who will be responsible for coordinating various aspects of the program in addition to supervising the in-house care provided in the intensive care unit. The director would also be responsible for assuring that the persons involved in the program are adequately trained and able to function as a surgical team on all occasions. We also recommend that a paid coordinator of nursing and allied health personnel be responsible for all nonphysician aspects of the in-hospital trauma program.

When one adds all the physician, nursing and allied health personnel costs we feel are necessary to staff such a community hospital trauma center, one arrives at an estimated annual cost of $1,682,-336 for such a program. We would estimate such a community hospital trauma program would need 400 to 500 trauma admissions per year in order to maintain skills.

It is apparent that whatever the trauma center or trauma program, the costs are high. Consumers cannot afford to pay for unnecessary trauma centers any more than they can afford to pay for unnecessary burn or neonatal care centers. How then does one estimate the need for trauma center development? Our review of the literature shows no clear discussion or guidelines to determine need. At least two states, Illinois and Maryland, have approached trauma care statewide; however, it is unclear if actual needs were determined in these

states; if so, how they were determined is also unclear. R. M. Gurfield, in a recent article in the *Journal of the American College of Emergency Physicians,*[9] delineated several indicators of need with respect to general emergency medical services, one of which was injury-producing automobile accidents. Serious motor vehicle accidents appear to be a stable forecaster, as they are the major source of multiple injuries in this country, with the exception of traumatic injuries such as gunshot and stab wounds in a few large urban areas. Using California as an example, we have developed what we believe to be a relatively simple and useful method for determining statewide need for trauma facilities.

Based on our review of data collected by the California Highway Patrol (CHP),[10] it would appear that each motor vehicle fatality results in an average of one patient requiring specialized trauma care, and that approximately 5 percent of all injured motor vehicle accident victims will require similar specialized trauma center care.[11] It is then a rather simple matter to take the readily available annual county-by-county CHP reports for motor vehicle accident victims who are killed or injured and multiply these figures by the aforementioned percentages to arrive at an indicator number for each county in the state.

From a purely mathematical standpoint, California can support 16 trauma centers or programs, each seeing no less than 1,000 seriously injured victims per year—the number recommended by the American College of Surgeons.

However, the obvious next step is to apply these mathematical indicators to known geographic and political boundaries. When this is done for California, it appears that the state could quite easily support 12 trauma centers or programs. It is also apparent that the population near the northern boundary of the state—around the Tahoe basin and in the eastern desert region—is best served by potential centers in Medford, Oregon, and in Reno, and Las Vegas, Nevada, respectively.

As stated previously, this scheme deals only with motor vehicle accidents. In large urban areas such as San Francisco and Los Angeles, the percentage of the trauma case load generated by sources other than motor vehicle accidents would need to be reviewed. Based on our experience, it is likely that these additional cases would not necessitate any increase in the number of trauma centers in either the two largest urban areas in California, simply because the comprehensive trauma centers in these areas will be able to handle case loads well in excess of 1,000 admissions per year.

We have attempted to deal rather pragmatically with some of the very real problems impeding the planning and development of regional trauma care centers. However, this presentation would be incomplete if mention were not made of the major impediment to such planning: regional and hospital politics. Each hospital wishes to see itself as a full-service institution fully capable of taking care of any and all problems. Most experienced emergency physicians feel that they can resuscitate almost any critically injured patient in their home hospitals. Most well-trained surgeons also feel that they are capable of treating such problems. Taking into account these factors plus the increasing number of unutilized hospital beds, there is little wonder that one becomes discouraged about the prospects for getting hospital administrators, emergency physicians and surgeons to work together and concentrate on giving optimal care to critically injured patients.

As awesome as the estimated staffing costs presented are, they are predicated on salary scales that are now five years old. Consequently, anyone planning to develop such trauma centers should expect to pay 10 percent to 20 percent more. We hope our presentation of a community hospital trauma program staffing pattern will precipitate some planning and critical thinking by those in areas of our country where large teaching hospital trauma programs are not available. But development of such trauma programs should not be undertaken without considering the factors discussed in relation to need. Only after determining actual need and applying a little common sense should one even begin preliminary planning for a trauma center.

DR. BLAISDELL: On the basis of all this information, it should be evident that organization of emergency services is urgently needed, with available emergency resources being concentrated in fewer hospitals for greater utilization and efficiency. An example of the type of planning that should be undertaken statewide is the emergency system plan we are now proposing for the City and County of San Francisco. In this proposal we have recommended that the public ambulance system, which heretofore has only transported patients to public hospitals, should be utilized to transport private patients to private hospitals as well, provided the

patient's physician is available or the receiving hospital has basic emergency room capabilities. However, if the transported patient's condition is unstable, we propose that he be transported to a district hospital. Although there are presently 18 hospitals in San Francisco, the total recommended number of hospitals to be designated as "district hospitals" is only three.

The requirements for such a district hospital would be the following.

- That it be capable of providing broad-spectrum emergency care—that is, that it can immediately and definitively treat major emergencies of every general type including neurosurgical, medical, pediatric, obstetrical and psychiatric, as well as trauma.
- That it have developed major emergency room capability as defined by the State of California Emergency Medical Plan.
- That it maintain an uncommitted operating room which is immediately available for any and all emergencies 24 hours a day.
- That it provide 24-hour laboratory and x-ray services, including the necessary in-house personnel to staff them.
- That it provide emergency staff privileges for any qualified physician in the region and allow him to assume responsibility for the management of his patients who are brought to the district hospital, provided he possesses the expertise to do so.
- That standard statistical records be kept and that these records documenting performance be made available to a regional director of emergency services and to the county Emergency Medical Care Committee for evaluation and review.
- That continued designation as a district hospital be contingent upon successful delivery of services comparable in quality to those delivered by the other district hospitals.

We further recommend that there be only one telemetry base station for the city of San Francisco. This conclusion is based on Department of Health, Education, and Welfare requirements which specify that there should be no more than *one* such base station for a population of one million. However, all receiving hospitals should be allowed to use the system to monitor and receive telemetry data on patients being transferred to their respective facilities.

We have also recommended that regionalization of emergency facilities be instituted, as recommended by the Department of Health, Education, and Welfare. This would entail consolidation of emergency services for Marin, San Francisco and San Mateo counties because they constitute a Health Service Area (HSA 4). The overall emergency care capabilities of the three counties should be reviewed as a whole and the need for cardiac centers, burn centers, trauma centers and drug information centers be assessed accordingly. Transfer and referral agreements among all the hospitals in these three counties should be developed to permit optimal utilization of the sophisticated facilities available in these metropolitan areas.

I feel very strongly that the medical profession should encourage measures such as these and should initiate them when and where we are able. If we do not, it will ultimately be done for us—and perhaps in a manner that our profession will not find either palatable or medically appropriate.

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

PRINCIPLES OF FAMILY MEDICINE—Robert E. Rakel, MD, Professor and Head, Department of Family Practice, University of Iowa College of Medicine, Iowa City, Iowa. W. B. Saunders Company, West Washington Square, Philadelphia, PA (19105), 1977. 536 pages, $14.75.

The author has accomplished far more than his stated purpose: "To provide a resource for medical students preparing for a future in Family Medicine." Actually, the book in essence is an exegesis of the development and present status of the family medicine concept or movement. Basic principles and measures of patient care in family medicine are accentuated. These are amply supported by many selected references, illustrative graphs and tables. Even reasons for including certain references are given—a most helpful innovation. Logically, much stress is placed on the broad aspects of family and patient care. Therefore, primary care and its continuation are goals, and individual illnesses kept in perspective. Sociobehavioral precepts, especially family dynamics, are underscored.

Good organization and a clear, easy style make the book very readable. Much wisdom is imparted, and numerous colorful, supportive quotes from early authoritative books and articles add weight to the opinions expressed.

Many in the traditional specialities may deny that family medicine is a discipline. Some will argue that the "percentages" of specialty care in family medicine are wrong or unrealistic. Others may repeat that family medicine has no universal claim to primary care. Nonetheless, the family medicine concept of a continuum of comprehensive medicine, with emphasis on the family unit as detailed in this book is a unique and effective contribution to health care.

A boon to medical students, but a bane to practicing physicians, is the unnecessarily exhaustive detail in the chapters "The Medical Record," "Family Charting" and "The Family Profile." Be this as it may, it is difficult to fault this excellent book, which may be a classic position-document for this newest major medical specialty.

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FAMILY MEDICINE—Principles and Applications—Edited by Jack H. Medalie, MD, MPH, Professor and Chairman, Department of Family Medicine, Case Western Reserve University School of Medicine, Cleveland. The Williams & Wilkins Company, 428 E. Preston Street, Baltimore (21202), 1978. 372 pages, $15.95.

Family Medicine—Principles and Applications should help put to rest those specialists who claim they are practicing family medicine because they serve as a triage officer for families mainly by directing family members to other specialties. The book puts the family into the center of family practice. It focuses on the discipline of family medicine emphasizing the sociological, epidemiological and psychosocial aspects of the family. It is an ecological approach, leaving the pathophysiology of disease to others.

Family Medicine attempts to define the discipline of family medicine and separates it from family practice. It discusses the family life cycle, family therapy, changing social patterns and the transmission of disease and health within the family. Consequently, the principles discussed are as useful to internists, pediatricians and obstetricians as they are to family physicians.

In the introduction and the first chapter, the authors make a courageous attempt to clarify the confusion existing among family medicine, family practice, primary care and general practice. But for the uninformed, their attempts fall a little short. And, the answer by the author of the introduction, Dr. Lynn Carmichael, to the question "What is Family Medicine?"—which is "Read Medalie"—doesn't do the trick either.

Medalie and contributors formalize much that an alert family physician learns and practices as he goes about his daily duties. It is surprising the sociological understanding a family physician acquires on his first 25 home calls. A physician who delivers babies, succors the dying, and aids unwed mothers and children failing in school learns family medicine rapidly. But he seldom thinks of this acquisition of knowledge as a separate formal discipline. It all becomes integrated into his background knowledge, and is subsequently shown in his attitudes and habits of treatment.

Family practice as is now being cast, should be examined in diverse ways. Dr. Medalie's text adds sociological, epidemiological and psychological dimensions to family practice. At present, the family practice movement has two needs: family medicine literature and qualified teaching personnel. Dr. Medalie's effort serves to satisfy the first and prepares personnel to meet the second.

The last few chapters discuss research, computers, nurses, social workers and the problem-oriented record system—all as related to family medicine. There are rather extensive chapter references taken from the literature of the last decade. And last of all, one finds a comprehensive author and subject index.

Family Medicine is a valuable text for family practice residents, and those internists and pediatricians interested in the health and welfare of families.

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ATLAS OF GRAY SCALE ULTRASONOGRAPHY—Kenneth J. W. Taylor, MD, PhD, Associate Professor, Department of Diagnostic Radiology, Yale University School of Medicine, New Haven, Connecticut. Churchill Livingstone—Medical Division, Longman Inc., 19 West 44th St., New York City (10036), 1978. 411 pages, $35.00.

Dr. Taylor defines his objectives in the preface of this excellent book: to provide an introduction to ultrasound for residents and practicing radiologists unfamiliar with the modality, to give an overview of the potential of ultrasound for referring physicians and to be of use to physicians already practicing ultrasound. It is a credit to the author that he succeeds in this broad spectrum of objectives.

The text begins with basic principles of ultrasound. It deals clearly and concisely with physics, instrumentation and varieties of scanning devices now in use. A chapter on practical aspects of scanning does provide practical information on the technical problems of generating useful scans. Illustrations of A mode scans used to adjust the TGC settings for proper B mode scans represent a valuable teaching tool. The next chapter outlines indications for scanning the liver and upper abdomen. A chapter on the liver considers normal anatomy, followed by a number of excellent case studies to portray a variety of disease conditions. High quality scans are clarified by

drawings with labels to identify the relevant anatomy and pathology. A number of isotope scans for correlation with the ultrasound study are included in this chapter. The book refers to computer assisted tomography (CAT) scanning from time to time, but does not undertake a similar correlation, either in regard to the liver or pancreas, or elsewhere. Subsequent sections consider the biliary system, the pancreas (by Bruce Simonds), the spleen (with Denise Moulton), the kidney (with Arthur Rosenfield), the great vessels, obstetrics, gynecology, the abdomen, the thyroid and the thorax.

There are very few faults to find in this work. Chapter 2 provides a table regarding patient preparation for ultrasound examination. It indicates that a gallbladder scan patient should have only water by mouth for the preceding eight hours, that a liver scan requires no special preparation, and that a pancreas scan should be done after the patient has eaten a light bland meal. Since it may be appropriate to scan more than one organ at the same session, this needs some clarification. In the pancreas chapter, Dr. Simonds makes the more conventional recommendation that a pancreas scan patient be examined fasting and early in the day.

The attractive organization of this atlas makes it seem deceptively simple, yet it will reward idle browsing or careful study. It is created by an outstanding practitioner of ultrasound and represents the state of the art. The neophyte may share our continuing wonder at the delicate structures which can be shown—small caliber arteries like the gastroduodenal or the arcuate arteries of the kidneys, the chambers of the fetal heart, or the discrimination between renal cortex and medulla. So for all of these reasons the book is recommended for any or all of the large group of readers to whom the author directs his message.

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HANDBOOK OF POISONING: Diagnosis & Treatment—Ninth Edition—Robert H. Dreisbach, MD, PhD, Clinical Professor of Environmental Health, School of Public Health and Community Medicine, University of Washington, Seattle, and Professor (Emeritus) of Pharmacology, Stanford University School of Medicine. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1977, 559 pages, $8.00.

One can hardly avoid mixed emotions on seeing a new edition of a well-established handbook. On the one hand is the anticipation of expanded and updated data, but on the other is the regret of parting with a cherished and well-thumbed friend in favor of the pristine stranger. Previous users of this handy pocket reference may allay their anxiety: the traditional format has been retained and the modest increase in thickness and mass will go undetected in the pocket. The rare neophyte who has never known the security of having this *Handbook* close to the telephone or to hand, will find an extensive section devoted to general considerations in the diagnosis and treatment of poisoning, serving as prologue to the detailed sections covering specific agricultural and medical poisons, and industrial, household, animal and plant hazards. All is tied together and made readily accessible by a comprehensive index, which successfully avoids being unwieldy without sacrifice of proprietary names of various insecticides and household products where such names offer no clue as to their toxic components. As in previous editions, the author concentrates on diagnosis and treatment rather than on chemistry and mechanisms of action; it is not a substitute for textbooks of toxicology and pharmacology. The reader is given suitable and current references to encourage deeper understanding as time permits.

The revision for this edition has been very thorough. Indeed, one might surmise that the author has had time for little else between editions. The changes range from the obvious to the subtle, often as slight as a change of emphasis in the components of a particular treatment regimen. The excellent reference lists, appearing at the end of each subsection within chapters, have been culled of older or less complete materials to permit the addition of more recent and relevant articles. Some lists have changed completely, with the sources rarely dated before 1973. Certain key references have been retained.

Treatments tend to reflect current, conservative medical practice. For example, a shift of priorities is evident in the management of pulmonary edema. Surgical intervention is now advocated after rattlesnake bites on the extremities. The growth of public and medical concern over environmental hazards has had its impact. There is a new subsection on the prevention of cancer, which, though surprisingly brief, embodies six useful references. Asbestos fiber shares this dubious public limelight and here there has been a doubling of references to 14. As the numbers of potential chemical toxins grow, so do their variety. In a table of miscellaneous pesticides, the majority being herbicides and fungicides, there are now 189 entries, more than double the number in the corresponding subsection of the previous edition. In contrast with the increasing complexity of tables resulting from the proliferation of new substances, it is refreshing to find that the table of toxic or lethal blood levels of drugs, has been simplified and made infinitely more legible without loss of critical information.

The Metrication Council should be proud of the consistent use of degrees Celsius, where previously temperatures had been given in Fahrenheit (with °C, somewhat apologetically, in parentheses). Nevertheless, for those of us in the transitional generation, it would have been comforting to see the familiar °F as well, even parenthetically.

Changes there are, but they add rather than detract from the fundamental utility of the *Handbook of Poisoning*, which is equally at home in the pocket of an emergency room physician or the desk of a pharmacologist-toxicologist. Few will fault it and all will make reference to it, no matter how extensive their personal libraries or experience.

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in memoriam

Barmore, Merrill G., Whittier. Died February 14, 1978, aged 76. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1930. Licensed in California in 1930. Dr. Barmore was a retired member of the Los Angeles County Medical Association.

Bender, William Lee, Mill Valley. Died September 22, 1978 in Mill Valley, aged 83. Graduate of the University of California Medical School, Berkeley-San Francisco, 1922. Licensed in California in 1922. Dr. Bender was a retired member of the San Francisco Medical Society.

Bordwell, Alden Shipp, Riverside. Died November 8, 1978 in Riverside, aged 73. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1930. Licensed in California in 1930. MD degree from California College of Medicine, 1962. Dr. Bordwell was a retired member of the Riverside County Medical Association.

Bowen, William P., L Jolla. Died November 1, 1978 in San Diego, aged 90. Graduate of Vanderbilt University School of Medicine, Nashville, 1915. Dr. Bowen was a retired member of the San Diego County Medical Society.

Castleberry, Malcolm L., Redding. Died April 18, 1978 of heart disease, aged 76. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1932. Licensed in California in 1932. MD degree from California College of Medicine, 1962. Dr. Castleberry was a member of the Santa Clara County Medical Society.

Caulkins, Charles Colgrove, Napa. Died September 21, 1978 in Napa of cardiac arrest, aged 76. Graduate of the University of California Medical School, Berkeley-San Francisco, 1936. Licensed in California in 1937. Dr. Caulkins was a retired member of the Napa County Medical Society.

Collins, Harry A., La Jolla. Died November 7, 1978 in La Jolla, aged 81. Graduate of the Creighton University School of Medicine, Omaha, 1922. Licensed in California in 1937. Dr. Collins was a retired member of the San Diego County Medical Society.

Dong, Eugene E., Salinas. Died November 11, 1978 in Los Angeles of cerebrovascular accident, aged 77. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1941. Licensed in California in 1941. MD degree from California College of Medicine, 1962. Dr. Dong was a member of the Monterey County Medical Society.

Gaede, David C., Palm Springs. Died December 3, 1977 of heart disease, aged 76. Graduate of Northwestern University Medical School, Chicago, 1937. Licensed in California in 1946. Dr. Gaede was a retired member of the Riverside County Medical Association.

Hohl, Elizabeth Mason, Los Angeles. Died November 4, 1978 in Los Angeles, aged 88. Graduate of the University of Nebraska College of Medicine, Omaha, 1915. Licensed in California in 1925. Dr. Hohl was a member of the Los Angeles County Medical Association.

Hurlbut, Jesse L. II, Sonoma. Died March 28, 1978 of heart disease, aged 72. Graduate of Columbia University College of Physicians and Surgeons, New York, 1931. Licensed in California in 1946. Dr. Hurlbut was a retired member of the Marin Medical Society.

Kuenkel, Victor H., Glendale. Died October 5, 1978 in Glendale, aged 66. Graduate of St. Louis University School of Medicine, 1943. Licensed in California in 1951. Dr. Kuenkel was a member of the Los Angeles County Medical Association.

Kushner, Neil J., Huntington Beach. Died November 12, 1978, aged 35. Graduate of Tufts University School of Medicine, Boston, 1972. Licensed in California in 1974. Dr. Kushner was a member of the Orange County Medical Association.

Larson, Albert Edwin, Hemet. Died March 20, 1978 in Hemet of arteriosclerosis, aged 87. Graduate of the College of Physicians and Surgeons, Los Angeles, 1918. Licensed in California in 1918. Dr. Larson was a retired member of the Los Angeles County Medical Association.

McDowell, Bruce E., Merced. Died August 8, 1978 in San Francisco, aged 81. Graduate of State University of Iowa College of Medicine, Iowa City, 1923. Licensed in California in 1929. Dr. McDowell was a retired member of the Merced-Mariposa Medical Society.

Osborn, Richard H., Monterey. Died May 7, 1978, aged 60. Graduate of the University of Washington School of Medicine, Seattle, 1951. Licensed in California in 1952. Dr. Osborn was a member of the Monterey County Medical Society.

Roberts, Arthur R., Fullerton. Died September 24, 1978, aged 50. Graduate of New York Medical College, Flower and Fifth Avenue Hospitals, New York, 1953. Licensed in California in 1954. Dr. Roberts was a member of the Orange County Medical Association.

Rogers, Arthur E. T., Palm Desert. Died July 5, 1978, aged 75. Graduate of Yale University School of Medicine, New Haven, 1927. Licensed in California in 1938. Dr. Rogers was an associate member of the Orange County Medical Association.

Zeifert, Mark, Fresno. Died November 1, 1978 in Merced of heart disease, aged 71. Graduate of St. Louis University School of Medicine, 1933. Licensed in California in 1945. Dr. Zeifert was a member of the Fresno-Madera Medical Society.

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WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

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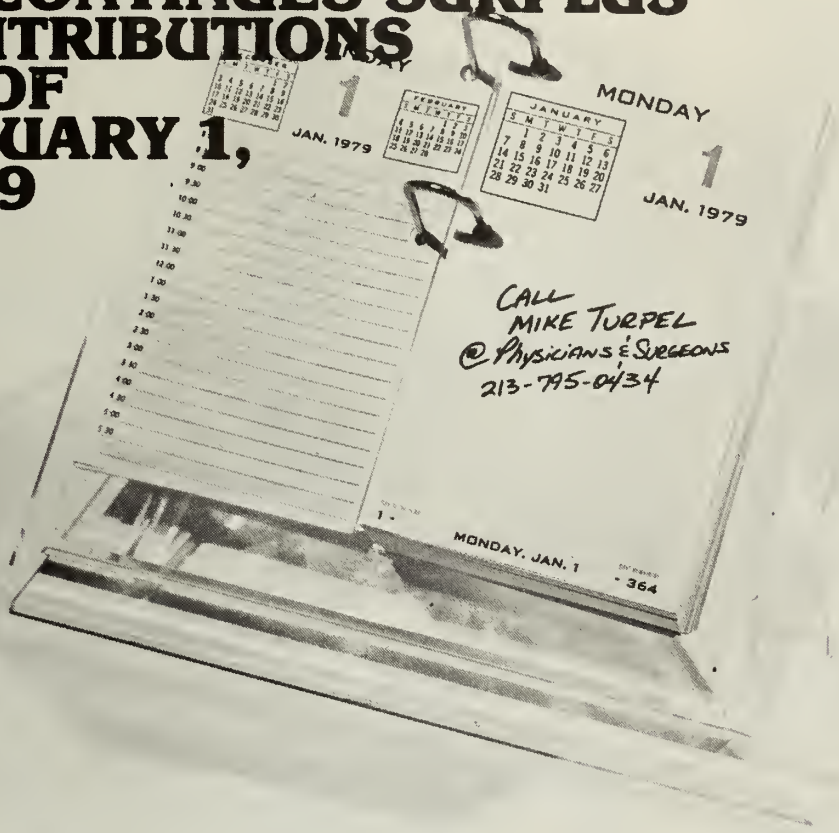

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(Continued from Page 22)

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(Continued on Page 26)

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(Continued from Page 25)

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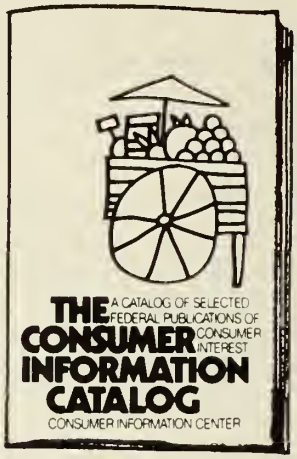
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ANESTHESIOLOGY

January 20-21—**American Society of Anesthesiologists—Workshop.** Sheraton-Island Hotel, San Diego. Saturday-Sunday. Contact: ASA, 515 Busse Highway, Park Ridge, IL 60068.

January 26-28—**Pediatric Anesthesiology—17th Clinical Conference.** Childrens Hospital of Los Angeles at Marriott Hotel, Los Angeles. Friday-Sunday. 15 hrs. $150. Contact: Wayne Herbert, MD, Prog. Dir., P.O. Box 54700, Los Angeles 90054. (213) 660-2450, ext. 2262.

February 11-13—**LLU Alumni Association Postgraduate Convention—Anesthesiology Section.** Sunday-Tuesday. Contact: Jerre K. Iversen, Exec. Dir., Alumni Assn. of the Sch. of Med., Loma Linda Univ., 1188 Anderson St., Loma Linda 92354. (714) 796-9537.

March 2-4—**Present and Future Clinical Use of Muscle Relaxants.** UCSF at Hyatt on Union Square, San Francisco. Friday-Sunday.

March 10-11—**Los Angeles County Society of Anesthesiologists—Postgraduate Assembly.** Hilton Hotel, Los Angeles. Saturday-Sunday. Contact: Virginia M. Connor, Exec. Sec., 184 N. Canon Dr., Beverly Hills 90210. (213) 275-4315.

March 18-23—**Anesthesiology 1979—5th Annual Winter Meeting.** Anesthesiology Educational Foundation and CSA at Mammoth Lakes. Sunday-Friday. Contact: Ronald L. Katz, MD, AEF, 3377 Colbert St., Los Angeles 90066.

April 20-22—**Newer Concepts and Older Practices in Obstetrical Anesthesia.** Fresno Community Hospital. Friday-Sunday. Contact: Joanne Ellis, Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

April 30-May 4—**California Society of Anesthesiologists—Hawaii Seminar.** Kauai Surf Hotel, Kauai. Monday-Friday. 20 hrs. Contact: CSA, Inc., 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

May 6-12—**16th Biennial Western Conference on Anesthesiology.** Sheraton Waikiki, Honolulu. One week. Contact: BWCA, 707-2525 Willow St., Vancouver, B.C., Canada V5Z 3N8.

May 31-June 4—**California Society of Anesthesiologists—Annual Scientific Meeting.** Disneyland Hotel, Anaheim. Thursday-Monday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

CANCER

January 20—**Gynecological Cancer.** SF Regional Cancer Foundation at Letterman Hospital, San Francisco. Saturday. 4 hrs. Contact: Norma Schlager, PhD, SF Regional Cancer Fnd., 14th and Lake, San Francisco 94118. (415) 221-2132.

January 26-27—**Cancer Seminar—2nd Annual.** Peralta Hospital at Claremont Hotel, Berkeley. Friday-Saturday. Contact: Tish Hammerlee, Peralta Hosp., 450 30th St., Oakland 94619. (415) 451-4900, ext. 269.

January 27-28—**Practical Oncology for the Primary Care Physician.** UCLA. Saturday-Sunday.

February 19-23—**Diagnosis and Management of the Complications of Cancer.** Scripps Clinic and Research Foundation at Holiday Inn at the Embarcadero, San Diego. Monday-Friday. 32 hrs. $280. Contact: Nomi Feldman, Box 705, La Jolla 92038. (714) 459-0511.

March 14-16—**Contemporary Gynecologic Oncology for the Practitioner.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

March 16—**Annual Cancer Symposium.** California Hospital Medical Center, Los Angeles. Friday. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

March 17—**Cancer Viewpoints No. 8—Thyroid Cancer Diagnosis and Treatment.** American Cancer Society, Contra Costa Unit, at John Muir Hospital, Walnut Creek. Saturday. Contact: ACS, Contra Costa Unit, 1341 Newell Ave., Walnut Creek 94596. (415) 934-7640.

March 23-24—**Body Image, Self-Esteem and Sexuality in Cancer Patients—14th Annual San Francisco Cancer Symposium.** West Coast Cancer Foundation and St. Mary's Hospital and Medical Center at Hyatt on Union Square, San Francisco.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

Friday-Saturday. $100 before Dec. 1; $125 after. Contact: Jerome M. Vaeth, MD, WCCF, 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

March 26-30—**Cancer.** STAN. Monday-Friday. 26½ hrs. $290.

April 7—**San Joaquin County American Cancer Society Conference—2nd Annual.** ACS, San Joaquin-Calaveras Unit, and San Joaquin Hospital at San Joaquin Delta College, Stockton. Saturday. 7 hrs. $25. Contact: ACS, San Joaquin-Calaveras Unit, 1111 W. Robinhood Dr., Stockton 95207.

May 12—**Genital Urinary Cancer.** San Francisco Regional Cancer Foundation at Fireman's Fund Building, San Francisco. Saturday. 4 hrs. Contact: Norma Schlager, PhD, S.F. Regional Cancer Fnd., 14th and Lake, San Francisco 94118. (415) 221-2132.

EMERGENCY MEDICINE

January 21-26—**Emergency Medicine.** UCLA at Beverly Hills Hotel. Sunday-Friday.

January 22-26—**Topics in Emergency Medicine.** UCSF at Sheraton, Fisherman's Wharf, San Francisco. Monday-Friday.

January 22-26—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Bahia Hotel, San Diego. Monday-Friday. 40 hrs. $350.

January 26-27—**Hand Injuries and Infections.** PMC. Friday-Saturday.

January 27—**Controversies in the Management of Pre-Hospital Cardiovascular Emergencies.** See Medicine, January 27.

January 29—**Narcotic Hydrocarbon and Acetaminophen Poisonings: An Overview and Current Treatment.** General Hospital Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at Gen. Hosp. Ventura Co., Ventura. Monday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

February 12-16—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 40 hrs. $350.

February 25-28—**Orthopedic Emergencies.** UCLA at Yosemite. Sunday-Wednesday.

February 25-March 2—**Emergency Medical Care Symposium.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. 27 hrs.

February 26—**Oral and Maxillofacial Trauma.** Gen. Hos. Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at Gen. Hosp., Ventura. Monday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

March 19-23—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Bahia Hotel, San Diego. Monday-Friday. 40 hrs. $350.

March 22—**Venous Animal Injuries.** General Hospital Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at Gen. Hosp., Ventura. Thursday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

April 2-6—**Medical Management of EMS Systems.** UCSD at Hilton, San Diego. Monday-Friday. 36 hrs. $120.

April 21-28—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 29 hrs. $325.

April 30—**Polyneuropathies.** General Hospital Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at General Hospital, Ventura. Monday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

May 7-11—**Topics in Emergency Medicine.** UCSF at Sheraton, Fisherman's Wharf, San Francisco. Monday-Friday.

May 14-18—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Islandia Hyatt House, San Diego. Monday-Friday. 40 hrs. $350.

May 21—**Hand Injuries.** General Hospital Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at General Hospital, Ventura. Monday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

May 26-June 2—**Annual Symposium on Diagnosis and Management of Medical Emergencies.** West Hills Hospital at Royal Lahaina Hotel, Maui, Hawaii. One week. 30 hrs. Contact: Charlotte McGuire, Adm. Coordinator, Medical Staff, West Hills Hosp., 7300 Medical Center Dr., Canoga Park 91307. (213) 884-7060, ext. 200.

MEDICINE

January 15—**Update on Clinical Electrocardiography.** Alta Bates Hospital at Holiday Inn, Emeryville. Monday. $25. Contact: Nursing Office, Alta Bates Hosp., 3001 Colby at Ashby, Berkeley 94705. (415) 845-7110, ext. 2123.

January 16-19—**Your Consultant Speaks.** STAN at Lake Tahoe. Tuesday-Friday. 12 hrs. $225; $100, residents. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

January 17-March 7—**Basic Electrocardiography for the Practicing Physician.** UCLA. Wednesdays; 7:30-9:30 p.m. 12 hrs. $235.

January 18-19—**Pulmonary Rehabilitation Symposium—2nd Annual.** Calif. Soc. for Respiratory Therapists, Chap. II; Lung Assns. of Riverside and San Bernardino Counties; Desert Hospital at Palm Springs. Thursday-Friday. Contact: CSRT, Chap. II, P.O. Box 683, Loma Linda 92354.

January 20—**Annual Cardiology Symposium.** Fresno Community Hospital. Tuesday. Contact: Joanne Ellis, Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

January 20-27—**Advances in Nephrology.** USC at Intercontinental Hotel, Maui, Hawaii. One week.

January 24—**Stroke and Hypertension.** American Heart Assn., Santa Clara Co. Chap., at Le Baron Hotel, San Jose. Wednesday. 6 hrs. $30. Contact: Harriet M. Schutte, RN, PhD, AHA, Santa Clara Co. Chap., 3003 Moorpark Ave., San Jose 95128.

January 24-26—**Advances in Neurology.** UCSF at Hyatt on Union Square, San Francisco. Wednesday-Friday.

January 26-28—**EKG Interpretation and Arrhythmia Management.** International Med. Education Corp. at Newporter Inn, Newport Beach. Friday-Sunday. 15 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

January 27—**Controversies in the Management of Pre-Hospital Cardiovascular Emergencies.** American Heart Assn., Greater LA Affiliate, and MICU Paramedic Training Institute at Hyatt House, Los Angeles. Saturday. 6 hrs. $50, HA member; $60, nonmember. Contact: AHA, Greater LA Affiliate, 2405 W. 8th St., Los Angeles 90057.

January 27-31—**American College of Allergists—35th Annual Congress.** Fairmont Hotel, San Francisco. Saturday-Wednesday. Contact: Frances P. White, ACA, 2141 14th St., Boulder, CO 80302. (313) 447-8111.

January 27-February 3—**Infectious Diseases in Clinical Practice—2nd Annual.** UCSF at Sun Valley, Idaho. One week. 21 hrs. $175.

January 31—**Rheumatoid Arthritis—A Discussion of Clinical Features and Attempts to Determine Its Etiology.** LA Soc. of Internal Medicine. Wednesday. 1 hr. Contact: Susan McNamara, LASIM, 8530 Wilshire Blvd., #313, Beverly Hills 90211. (213) 659-6750.

(Continued on Page 30)

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General lectures will cover a review of chemistry and physics for clinicians, chemical bonds of biological importance, subatomic particles, correlation of cell structure and function, the structure and function of proteins, sugars and lipids, the structure of nucleic acids, DNA synthesis, expression and organization of genetic information, regulation of gene expression, gene manipulation, carbohydrate and fat metabolism, bioenergetics, membrane structure, the organization and function of the brain.

Elective sessions will include the evolution of proteins, the discovery of particles with charm, bacterial antibiotic resistance, structure and function of heterochromatin, cellular and humoral mechanisms of immunity, human evolution, mediators of inflammation and immunity, mitochondria and related diseases, nutrition, association between HL-A and various disease states, nerve growth factors, demonstration of electric signalling by nerve cells.

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MARCH 11-13, 1979

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(Continued from Page 28)

January 31-February 2—**Brain Injury.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

February 2-4—**New Concepts in Clinical Electrocardiography.** American College of Cardiology and Cedars-Sinai Medical Center at Beverly Hilton Hotel, Beverly Hills. Friday-Sunday. Contact: Mary Anne McInerny, Dir., Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 3—**Pulmonary Artery Catheters.** PMC. Saturday.

February 3—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

February 7-9—**Internal Medicine for the Primary Care Physician.** UCD at Harrah's, Lake Tahoe. Wednesday-Friday.

February 12-15—**Current Concepts, Controversies and Clinical Strategies in Gastroenterology.** Cedars-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Monday-Thursday. 26 hrs. $350. Contact: Leslie J. Schoenfield, MD, Dir., Dept. of Gastroenterology, Cedars-Sinai Med. Ctr., Box 48750, Los Angeles 90048. (213) 885-6146.

February 14-16—**Cardiovascular Disease—1979: Advances in Diagnosis and Therapy.** American College of Cardiology at Sheraton Harbor Island, San Diego. Wednesday-Friday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

February 15-16—**Pulmonary Function Evaluation: Clinical Application of New Techniques.** Memorial Hospital Medical Center, Long Beach. Thursday-Friday. 12 hrs. $150. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 17—**Viral and Viral-Like Lesions of the Liver.** Memorial Hospital Medical Center, Long Beach. Saturday. 8 hrs. $105. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 17—**Perspectives in Immune and Hypersensitivity Lung Disease—5th Annual Pulmonary Symposium.** USC and Inter-Community Hospital at Calif. Polytechnic Univ., Pomona. Saturday. 5 hrs. $25. Contact: Gregg Masters, Inter-Community Hosp., 303 N. 3rd Ave., Covina 91723. (213) 331-7331, ext. 2623.

February 21-23—**Daily Decisions in Lung Disease—Annual Postgraduate Course.** Calif. Thoracic Society at Red Lion Motor Inn, Sacramento. Wednesday-Friday. 16 hrs. $160, members; $180, nonmembers. Contact: Anna B. Roberts, Admin. Asst., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

February 24—**Workshop in Complex Arrhythmias.** PMC. Saturday.

February 24-25—**Dermatology, Allergy and Immunobiology.** UCLA. Saturday-Sunday. 14½ hrs. $150.

March 2-3—**Neuromuscular Disease.** PMC. Friday-Saturday.

March 6-10—**Consultant's Course in Dermatology—7th Annual.** UCSF. Tuesday-Saturday.

March 7—**The Role of Radioimmunoassay in Clinical Medicine.** LA Soc. of Internal Medicine. Wednesday. 1 hr. Contact: Susan McNamara, LASIM, 8530 Wilshire Blvd., #313, Beverly Hills 90211. (213) 659-6750.

March 10-11—**Nuclear Medicine.** See Radiology and Pathology, March 10-11.

March 11-14—**Topics in Gastroenterology.** UCSF at Yosemite. Sunday-Wednesday.

March 23-25—**Cardiac Symptoms, Arrhythmias and Holter Monitoring.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

March 26-28—**Occupational Skin Diseases.** UCSF. Monday-Wednesday.

March 26-29—**American College of Physicians—60th Annual Session.** San Francisco. Monday-Thursday. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

March 26-April 6—**Intensive Review of Internal Medicine.** USC. Two weeks.

March 29-30—**International Symposium on the Larynx.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Friday.

March 29-30—**Cardiovascular Nuclear Medicine—Current Concepts and Their Clinical Applications.** Foundation for Cardiovascular Research and Peralta Hospital at Stanford Court Hotel, San Francisco. Thursday-Friday. 12 hrs. Contact: FCR, 201 N. El Molino, Suite 100, Pasadena 91101.

March 29-31—**Contemporary Management of Acute Myocardial Infarction by the Family Physician.** American College of Cardiology and American Academy of Family Physicians at Riviera Hotel, Palm Springs. Thursday-Saturday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 29-31—**International Symposium on Contact Dermatitis.** UCSF. Thursday-Saturday.

April 2-11—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 4—**Antimicrobial Therapy: The State of the Art.** L.A. Society of Internal Medicine. Wednesday. 1 hr. Contact: Susan McNamara, LASIM, 8530 Wilshire Blvd., No. 313, Beverly Hills 90211. (213) 659-6750.

April 4-June 6—**Rheumatology.** UCLA. Wednesday evenings.

April 11-13—**Review and Updating of the Immunology and Clinical Practice of Allergy—3rd Annual.** UCSD at Hilton Hotel, San Diego. Wednesday-Friday.

April 18—**Society of Nuclear Medicine, Southern California Chapter.** See Radiology and Pathology, April 18.

April 21—**Flexible Fiberoptic Bronchoscopy.** PMC. Saturday. 6 hrs. $325.

April 27—**Controversies in Cardiology.** American Heart Assn., Santa Clara County Chapter, at Le Baron Hotel, San Jose. Friday. 6 hrs. $30. Contact: Harriet M. Schutte, RN, PhD, AHA, Santa Clara Co. Chap., 3003 Moorpark Ave., San Jose 95128.

May 3-5—**Critical Care Cardiology.** PMC. Thursday-Saturday. 18 hrs.

May 4-6—**Sierra Valley Nuclear Medicine Association.** See Radiology and Pathology, May 4-6.

May 4-6—**Coronary Disease, Exercise Testing and Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton Inn, San Diego. Friday-Sunday. 13 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

May 5—**Pediatric Dermatology Serminar.** STAN. Saturday. 7 hrs. $75. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

May 11—**Bay Area Vascular Society.** UCSF at Mark Hopkins, San Francisco. Friday.

May 11-13—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Sunday. 15 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

May 12—**Controversies in Internal Medicine—3rd Annual Program.** San Jose Health Center at Marriott's Great America, Santa Clara. Saturday. 6 hrs. $40. Contact: Stanley Skillicorn, MD, Dir. of Med. Ed., San Jose Health Ctr., 675 E. Santa Clara, San Jose 95112. (408) 998-3212.

May 12-13—**Venous Thrombosis and Embolism.** UCLA. Saturday-Sunday. 14 hrs.

OBSTETRICS AND GYNECOLOGY

January 18-May 24—**Decision Making in Obstetrics and Gynecology.** UCLA. Thursdays. 34 hrs. $310.

February 3-9—**Perinatal Medicine.** USC at Royal Lahaina, Maui, Hawaii. One week.

March 8-9—**Practical Options in Perinatal Health Care.** UCD at Hyatt Lake Tahoe. Thursday-Friday. 8½ hrs. $100.

March 14-16—**Contemporary Gynecologic Oncology for the Practitioner.** See Cancer, March 14-16.

March 14-16—**Basic and Advanced Gyn Urology.** Women's Hospital of Long Beach, Memorial Hospital and Medical Center of Long Beach, UCI at Inn at the Park, Anaheim. Wednesday-Friday. 20 hrs. $300. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801.

April 15-21—**Current Dialogues in Obstetrics and Gynecology.** Memorial Hospital Medical Center of Long Beach and Women's Hospital of Long Beach at Kauai Surf, Kalapaki Beach, Hawaii. One week. 22 hrs. $300. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 21-23—**Recent Advances in Obstetrics and Gynecology.** UCSD at Vacation Village, San Diego. Monday-Wednesday.

PEDIATRICS

January 21-24—**Winter Ski and Study Symposium—4th Annual.** American Academy of Pediatrics, Calif. Chap. 2, at Mammoth Mountain. Sunday-Wednesday. Contact: Eve Black, AAP, Calif. Chap. 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

January 27—**Cardiology for the Pediatrician.** Kaiser-Permanente, Sacramento, at Kaiser Center, Oakland. Saturday. 5 hrs. $30. Contact: Onera Roberts, Staff Education, Kaiser Foundation Hosp., 2025 Morse Ave., Sacramento 95825. (916) 486-5965.

February 10-11—**Pediatrics for the Primary Physician—2nd Annual Review.** UCLA. Saturday-Sunday. 10¾ hrs. $145.

February 22-24—**Update on Pediatric Hematology—Annual Winter Meeting.** Children's Hospital Medical Center, Oakland, at Sahara Hotel, Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes, Med. Staff Office, CHMC, 51st and Grove Sts., Oakland 94609.

March 15-18—**Clinical Pediatrics—Combined Southern California Pediatric Postgraduate Meeting.** American Academy of Pediatrics, Calif. Chap. 2, at Riviera Hotel, Palm Springs. Thursday-Sunday. Contact: Eve Black, AAP, Calif. Chap. 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

April 6-7—**Practical Pediatric Endocrinology.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 9 hrs. $65.

May 7-11—**Pediatric Review—9th Annual.** USC. Monday-Friday.

May 10-12—**Annual Pediatric Course.** UCSF. Thursday-Saturday.

May 12-19—**Pediatric Workshop.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

PSYCHIATRY

January 15-18—**Working with the Victims of Sexual Assault and Violent Crimes.** Mental Research Institute, Palo Alto. Monday-Friday. $75. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 19-21—**Perspectives on the Self: A Multidisciplinary Approach.** See Of Interest To All, January 19-21.

January 20—**Brain Evoked Potentials: Clinical Applications.** Institute for Medical Research, Santa Clara Valley Medical Center, Langley Porter Institute at Santa Clara Valley Med. Ctr., San Jose. Saturday. 6 hrs. $125. Contact: IMR, 751 S. Bascom Ave., San Jose 95128. (408) 998-4554, ext. 15.

January 23-26—**Family Interactional Psychotherapy: Processes and Practices.** Mental Research Institute, Palo Alto. Tuesday-Friday. $140. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301. (415) 321-3055.

January 29-February 2—**Mid-Winter Program in Continuing Education for Psychiatrists—5th Annual.** UCD at Hyatt Lake Tahoe, Incline Village. Monday-Friday. 26 hrs. $150.

January 30—**Continuing Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

February 1-4—**Pathways to Adulthood—5th Reunion of the Pan American Forum for the Study of Adolescence.** American Society for Adolescent Psychiatry at Fairmont Hotel, San Francisco. Thursday-Sunday. 18 hrs. Contact: Philip C. Gradolph, MD, 1603 Orrington, Suite 1050, Evanston, IL 60201.

February 16-17—**Violence: What's Happening!—5th National Seminar.** Vista Hill Foundation at Hotel del Coronado, Coronado. Friday-Saturday. Contact: Keith S. Ditman, MD, Vista Hill Fnd., 7798 Starling Dr., San Diego 92123. (714) 278-6761.

February 22-25—**Sixth International Gender Dysphoria Symposium.** See Surgery, February 22-25.

February 23-24—**Psychiatric Aging.** UCD at Hyatt Lake Tahoe, Incline Village. Friday-Saturday.

February 27—**Continuing Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

March 17-19—**Psychiatrist as a Primary Care Physician.** USC at Rancho Bernardo, San Diego. Saturday-Monday.

March 27—**Continuing Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

April 7, 21—**The Family as Patient: Case Studies in Family Therapy.** UCLA. Two Saturdays.

April 24—**Continuing Medical Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

May 29—**Continuing Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

RADIOLOGY AND PATHOLOGY

January 17-19—**Workshop on Physics and Engineering Problems in Computerized Tomography.** UCI at Newporter Inn, Newport Beach. Wednesday-Friday.

January 21-26—**Skeletal Symposium—2nd Annual.** UCSF at Sun Valley, Idaho. Sunday-Friday.

January 24-26—**Genitourinary Pathology—6th Annual Course.** Memorial Hospital Medical Center, Long Beach. Wednesday-Friday. 23 hrs. $200. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 26-28—**31st Annual Midwinter Radiological Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. $125. Contact: Earl P. Detrick, MD, 4415 Lakeview Canyon Rd., Westlake Village 91361.

January 27-28—**Radiology Conference.** UCSF at Hyatt on Union Square, San Francisco. Saturday-Sunday.

January 29-February 2—**Computed Tomography, Ultrasound and X-ray.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

February 3-4—**Radiology.** UCSF. Saturday-Sunday.

February 5-9—**Tutorial on Neoplastic Hematopathology.** City of Hope National Medical Center and Univ. of Chicago Center for Continuing Education at Huntington-Sheraton Hotel, Pasadena. Monday-Friday. 40 hrs. $700. Contact: Mr. Claude M. Weil, Asst. Dir., Ctr. for Cont. Ed., 1307 E. 60th St., Chicago 60637. (312) 753-3186.

February 7-9—**Selected Topics in Neuroradiology.** San Diego Radiology Research and Education Foundation and American College of Radiology at San Diego. Wednesday-Friday.

22½ hrs. $225. Contact: Mary J. Ryals, Radiology, P.O. Box 2305, La Jolla 92038. (714) 453-7500, ext. 3711.

February 12-15—**Third Annual Symposium on the Molecular Basis of Cell-Cell Interaction.** Scripps Clinic and Research Foundation at Islandia Hyatt House, San Diego. Monday-Thursday. 24 hrs. $125. Contact: Nomi Feldman, Box 705, La Jolla 92038. (714) 459-0511.

February 14—**Society of Nuclear Medicine, Southern California Chapter, Dinner Meeting.** LA Co. Med. Assn. Headquarters, Los Angeles. Wednesday. Contact: Jean Lynch, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

March 9-11—**Gastrointestinal Radiology, Update '79.** San Diego Radiology Research and Education Foundation and ACR at San Diego. Friday-Sunday. 18 hrs. $200. Contact: Mary J. Ryals, Radiology, P.O. Box 2305, La Jolla 92038. (714) 453-7500, ext. 3711.

March 10-11—**Pediatric Radiology.** UCSF at Hyatt on Union Square, San Francisco. Saturday-Sunday.

March 10-11—**Nuclear Medicine.** UCSF at Hyatt on Union Square, San Francisco. Saturday-Sunday.

March 12-16—**Diagnostic Radiology.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday. 33 hrs. $300.

March 17-18—**Ultrasound.** UCSF at Hyatt on Union Square, San Francisco. Saturday-Sunday.

March 29-30—**Cardiovascular Nuclear Medicine.** See Medicine, March 29-30.

May 3-4—**Radiology Seminar—Clinical Problems.** UCSF. Thursday-Friday.

May 4-6—**Sierra Valley Nuclear Medicine Association—11th Annual Spring Symposium.** Northern Calif. Chapter, Society of Nuclear Medicine, at MGM Grand Hotel, Reno. Friday-Sunday. Contact: Cathy Suey, Nuclear Medicine, 4301 X St., Sacramento 95817.

April 7—**Imaging.** UCLA. Saturday.

April 18—**Society of Nuclear Medicine, Southern California Chapter—Annual Benedict Cassen Memorial Lecture Dinner Meeting.** L.A. Co. Med. Assn. Headquarters, Los Angeles. Wednesday. Contact: Jean Lynch, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

April 19-20—**Radiology Seminar—Clinical Problems.** UCSF. Thursday-Friday.

May 3-4—**Radiology Seminar—Clinical Problems.** UCSF. Thursday-Friday.

May 19—**Radiology Symposium.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7½ hrs. $50.

May 19-20—**Pathology of the Endocrine System.** UCLA at Long Beach Convention Center. Saturday-Sunday.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 15 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

January 15-19—**Otologic Surgery Course—14th Annual.** Ear Research Institute, Los Angeles. Monday-Friday. 40 hrs. $500. Contact: F. H. Linthicum, Jr., MD, ERI, 256 S. Lake St., Los Angeles 90057.

January 19-20—**The Western Hair Transplant Seminar.** American Academy of Facial Plastic and Reconstructive Surgery and USC at Bonaventure Hotel, Los Angeles. Friday-Saturday. Contact: USC.

January 20—**Postgraduate Course in Surgery.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7 hrs. $50.

January 21-25—**Ophthalmology and Otolaryngology—48th Annual Mid-Winter Clinical Convention.** Research Study Club at Hilton Hotel, Los Angeles. Sunday-Thursday. 28 hrs. Contact: Richard Pruter, Exec. Sec., RSC, P.O. Box 49412, Los Angeles 90049. (213) 879-0648.

January 22-25—**Assembly in Surgery—2nd Annual.** Surgical Ed. and Research Fnd.; Am. College of Surgeons, San Diego Chap.; Soc. of Gen. Surgeons of San Diego at Islandia Hyatt House, San Diego. Monday-Thursday. 32 hrs. $300. Contact: Nomi Feldman, Box 705, La Jolla 92038. (714) 459-0511.

January 26-27—**Vitrectomy Workshop.** PMC at Tripler Hospital, Honolulu. Friday-Saturday.

January 27—**Ophthalmic Plastic Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Jules Stein Eye Inst., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

January 31-February 2—**Acute Brain Injury.** See Medicine, January 31-February 2.

February 2-3—**Head Trauma Rehabilitation Conference.** Santa Clara Valley Medical Center, San Jose. Friday-Saturday. Contact: Head Injury Rehab. Proj., Santa Clara Valley Med. Ctr., 751 S. Bascom Ave., San Jose 95128.

February 5-9—**Theodor Billroth Course in Surgical Anatomy—20th Annual.** LLU. Monday-Friday. 32 hrs. $250.

February 7-9—**Flaps and Grafts.** UCLA. Wednesday-Friday. 24 hrs. $300.

February 15-16—**Corneal and External Disease.** UCSF. Thursday-Friday.

February 22-25—**Sixth International Gender Dysphoria Symposium.** UCSD at Hotel del Coronado, Coronado. One week.

February 23-24—**Phacoemulsification Surgery Course.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $300. Contact: Lu Hendricks, Jules Stein Eye Inst., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

February 25-28—**Orthopedic Emergencies.** See Emergency Medicine, February 25-28.

March 9-10—**Ophthalmology Update I.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. $225.

March 10-14—**Controversial Areas in Surgery.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday

March 14-16—**Basic and Advanced Gyn Urology.** See Obstetrics and Gynecology, March 14-16.

March 14-18—**Vascular Surgery.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 17—**Cataract Surgery and Intraocular Lens Implantation Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Mrs. Lu Hendricks, Jules Stein Eye Inst., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

March 23-25—**Workshop in Soft Tissue Surgery.** UCI. Friday-Sunday.

March 26-30—**Head and Neck Surgery.** USC. Monday-Friday.

March 29-30—**International Symposium on the Larynx.** See Medicine, March 29-30.

March 29-30—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

April 3-7—**General Surgery.** UCSF at Sheraton Palace, San Francisco. Tuesday-Saturday.

April 8-11—**U.S. Intraocular Lens Symposium.** American Intraocular Implant Society at Century Plaza Hotel, Los Angeles. Sunday-Wednesday. Contact: Kenneth J. Hoffer, MD, P.O. Box 3140, Santa Monica 90403.

April 13-14—**Operative Arthroscopy.** UCLA. Friday-Saturday. 12¼ hrs. $315.

April 18-20—**Vitrectomy.** UCSF. Wednesday-Friday.

April 19-20—**Neuro-Ophthalmology—10th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. 16 hrs. $225. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Inst., UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

April 19-21—**Wound Management Workshop.** UCSD, Div. of Plastic Surgery, at Islandia Hyatt House, San Diego. Thursday-Saturday.

May 17-18—**Office Orthopedics.** USC. Thursday-Friday.

May 26—**Retinal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Jules Stein Eye Inst., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

May 31-June 1—**Neurosurgery—9th Annual Postgraduate Course.** UCSF at Hilton Hotel, San Francisco. Thursday-Friday.

OF INTEREST TO ALL PHYSICIANS

January 15-19—**Chemical Dependency: A Family Disease.** UCI and Memorial Hospital Medical Center, Long Beach. Monday-Friday. 20 hrs. $250. Contact: Center for Health Education, Memorial Hosp. Med. Ctr., 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

January 19-21—**American Medical Association—Regional Program.** MGM Grand Hotel, Reno. Friday-Sunday. Contact: UCD.

January 19-21—**Perspectives on the Self: A Multidisciplinary Approach.** UCSF. Friday-Sunday.

January 20—**Institute on Autoimmune Disease.** CME-SLO Consortium at Cuesta College, San Luis Obispo. Saturday. 5 hrs. $25 for non-consortium members. Contact: CME-SLO Consortium, P.O. Box 319, San Luis Obispo 93406.

January 20—**Brain Evoked Potentials: Clinical Applications.** See Psychiatry, January 20.

January 22-27—**Family Practice Refresher Course.** UCI at South Coast Plaza Hotel, Costa Mesa. One week. 46 hrs.

January 22-26—**Therapy: Principles and Use of Drugs.** STAN. Monday-Friday. 27 hrs. $290.

January 24-26—**Prevention of Winter Sports Injuries—8th Annual Conference.** Sierra Traumatological Society at Bear Valley. Wednesday-Friday. 6 hrs. $50. Contact: STS, P.O. Box 230, Stockton 95201. (209) 466-9535.

January 25-28—**Winter Postgraduate Institute.** CMA and UCSF at Lakeland Village, Lake Tahoe. Wednesday-Saturday. Contact: Charlotte Newhart, CMA. 13 hrs.

January 27—**Total Parenteral Nutrition.** UCLA. Saturday. 7 hrs. $80.

January 27-28—**Practical Oncology for the Primary Care Physician.** See Cancer, January 27-28.

January 27-28—**Scientific Seminar—17th Annual.** David M. Brotman Memorial Hospital at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. Contact: Daniel A. Lang, MD, Med. Dir., Brotman Mem. Hosp., 3828 Delmas Terrace, Culver City 90230. (213) 836-7000.

January 29-February 2—**Immunology for the Practicing Physician.** Scripps Clinic and Research Foundation at Islandia Hyatt House, San Diego. Monday-Friday. 35 hrs. $300. Contact: Nomi Feldman, Box 705, La Jolla 92038. (714) 459-0511.

February 3—**Institute on Immunology.** CME-SLO Consortium at Cuesta College, San Luis Obispo. Saturday. 4 hrs. $25, nonmembers. Contact: CME-SLO Consortium, P.O. Box 319, San Luis Obispo 93406.

February 3-4—**Human Immunobiology for the Primary Care Physician.** UCLA. Saturday-Sunday. 14 hrs. $150.

February 3-10—**Hypnosis and Imagery: Practical Applications.** Bay Gen. Community Hospital at Sun Valley, Idaho. One week. Contact: Errol Korn, MD, 480 4th Ave., Suite 409, Chula Vista 92010. (714) 420-8051.

February 5-8—**Critical Care Medicine.** USC at MGM Grand Hotel, Las Vegas. Monday-Thursday.

February 7-10—**Primary Care: Current Management of Common Office Problems.** UCSF at Golden Gateway Holiday Inn, San Francisco. Wednesday-Saturday.

February 9-15—**LLU Alumni Association—47th Annual Postgraduate Convention.** One week. Contact: Jerre K. Iversen, Alumni Assn. of Sch. of Med., LLU, 1188 Anderson St., Loma Linda 92354. (714) 796-9537.

February 10-11—**Pediatrics for the Primary Physician—2nd Annual Review.** See Pediatrics, February 10-11.

February 14-16—**29th Annual Course for Physicians in Family Practice.** Mt. Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Office of Cont. Ed., Mt. Zion Hosp. and Med. Ctr., P.O. Box 7921, San Francisco 94120.

February 15-December 13—**Differential Diagnosis.** USC. 8 Thursdays.

February 21-23—**Human Chlamydial Infection and Associated Sexually Transmitted Diseases.** UCSF. Wednesday-Friday.

February 25-March 2—**International Society for Clinical Enzymology.** UCSD at Sheraton Harbor Hotel, San Diego. Sunday-Friday.

February 26-March 2—**Basic Science for Clinicians.** STAN. Monday-Friday. 25½ hrs. $290.

March 2—**Diabetes Program—6th Annual.** UCD at Red Lion Motor Inn, Sacramento. Friday. 6½ hrs. $45.

March 6-10—**Sports Medicine.** Univ. of Hawaii and AAFP at Princess Kaiulani Hotel, Waikiki, Honolulu. Tuesday-Saturday. 18 hrs. $200. Contact: Hawaii Conference Services. P.O. Box 25055, Honolulu 96825. (808) 377-6445.

March 8-10—**Neurology for Non-Neurologists.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday. 21 hrs.

March 9-10—**Workshop on Aging.** UCD at Hyatt Lake Tahoe, Incline Village. Friday-Saturday. 8 hrs. $85.

March 9-14—**California Medical Association—108th Annual Session.** Bonaventure Hotel, Los Angeles. Friday-Wednesday. Contact: Rocki Lai, CMA.

March 11-15—**The Patient—The Physician—The Process: Appropriate Medicine 1979.** UCLA at Asilomar, Monterey. Sunday-Thursday.

March 14-18—**Preventive Interventions in Medicine: Prenatal to Postmenopause.** Eisenhower Medical Center at Marriott Las Palmas Resort, Rancho Mirage. Wednesday-Sunday. Contact: John J. Deller, MD, Dir. of Ed. and Research, EMC, 39000 Bob Hope Dr., Palm Desert 92260. (714) 346-3911.

March 15-17—**Practical Psychiatry for Primary Practitioners.** PMC. Thursday-Saturday.

March 18-22—**Current Issues in Sexuality in Medical Practice.** UCSF at Yosemite. Sunday-Thursday.

March 22-25—**Basic Clinical Hypnosis Workshop—3rd Annual.** UCI at Balboa Bay Club, Newport Beach. Thursday-Sunday.

March 29-31—**Contemporary Management of Acute Myocardial Infarction by the Family Physician.** See Medicine, March 29-31.

March 31-April 1—**Obesity.** UCLA. Saturday-Sunday.

March 31-April 1—**Symposium on Aging—2nd Annual.** UCSF at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF, Cont. Ed. in Health Sciences, 1343 3rd Ave., San Francisco 94143. (415) 666-3904.

April 5-7—**West Coast Counties Postgraduate Institute.** CMA and UCD at Doubletree Inn, Monterey. Thursday-Saurday. 13 hrs. $60, CMA members; $90, nonmembers. Contact: Charlotte Newhart, CMA.

April 19-21—**San Joaquin Valley Counties Postgraduate Institute.** CMA and UCSD at Ahwahnee Hotel, Yosemite. Thursday-Saturday. 14 hrs. $60, members; $90, nonmembers. Contact: Charlotte Newhart, CMA.

April 21-22—**Health Care Maintenance.** UCLA. Saturday-Sunday.

April 23-25—**The Body Fluids in Health and Disease.** UCSF. Monday-Wednesday.

April 28-May 5—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $325.

May 13-18—**Fingers-to-the-Toes: An Orthopedic Approach for the Family Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf. Sunday-Friday. 40 hrs. $225.

May 15-21—**Diving Medicine, Basic.** UCSF at VA Hospital, Fresno. One week.

May 18-19—**UCSF—Alumni Day Program.** Friday-Saturday.

May 25-26—**Imported Tropical Disease: Current Views on Therapy and Epidemiology.** UCSF. Friday-Saturday.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

OREGON

COUNCIL ON MEDICAL EDUCATION

THIS BULLETIN of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, 97213.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

February 12-16—**Tenth Annual Family Practice Review.** Sheraton Hotel, Lloyd Center, Portland. Contact: J. S. Reinschmidt, MD, Director of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

Circuit Course Programs—Contact: Joyce Gullixson, Oregon Medical Association, 5210 SW Corbett Avenue, Portland 97201.

January 18 (Newport)—**Dizziness/Syncope, Loss of Consciousness.** New Lincoln Hospital, 1:30 p.m.

January 24 (Medford)—**Vascular Problems and Pulmonary Emboli.** Providence Hospital, 1:30 p.m.

February 7 (Klamath Falls)—**Back Problems.** Presbyterian Intercommunity Hospital, 1:30 p.m.

February 8 (Bend)—**Back Problems.** St. Charles Hospital, 1:30 p.m.

March 1 (Pendleton)—**Office Psychiatric Problems.** St. Anthony Hospital, 1:00 p.m.

March 8 (Astoria)—**Office Gynecology.** Columbia Memorial Hospital 1:30 p.m.

April 11 (Roseburg)—**Urology.** Douglas Community Hospital, 1:30 p.m.

April 12 (Coos Bay)—**Urology.** Thunderbird Courtel, 1:30 p.m.

February 11—**March of Dimes Symposium.** Red Lion, Jantzen Beach, Portland. Contact: J. S. Reinschmidt, MD, Director of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

March 9-10—**Breast Cancer.** Salishan Lodge, Gleneden Beach. Contact: Myrna Glenn, American Cancer Society, 910 NE Union, Portland 97232.

March 30-April 1—**Endocrinology.** Salishan Lodge, Gleneden Beach. Contact: J. S. Reinschmidt, MD, Dept. of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

April 19-20—**Dermatology for the Non-Dermatologist.** Red Lion, Jantzen Beach, Portland. Contact: J. S. Reinschmidt, MD, Dept. of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

April 26-27—**Oregon Heart Association Annual Scientific Session.** Red Lion, Portland Center, Portland. Contact: Audrey Booth, Oregon Heart Association, 1500 SW 12th Avenue, Portland 97201.

WASHINGTON

Beginning with the February issue, programs listed in this section will be compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, No. 900, Seattle 98121; or phone (206) 623-4801.

January 19-20—**American Society of Parenteral and Enteral Nutrition: Nutritional Support of the Hospitalized Patient.** Friday-Saturday. Virginia Mason Medical Center, Seattle. Contact: Frederick Fenster, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

January 22-23—**An Approach to Cutaneous Manifestations of Internal Malignancy—Univ. of Wash. Internal Medicine Review Sessions in Washington.** Monday, Jan 22, Wenatchee. Contact: William M. McKee, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711. Tuesday, Jan 23, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

January 26-27—**Eye Care in the Medical Practice.** Friday-Saturday. Virginia Mason Medical Center Auditorium, Seattle. Contact: Frederick Fenster, MD, Dir. CME, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

ALASKA, MONTANA AND IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

February 8—**Cross-Cultural Approaches in Psychiatric Care and Mental Health—Univ. of Wash. Psychiatry Sessions.** Thursday. Anchorage. Contact: Robert F. Kraus, MD, Star Route A, Box 26-B, Anchorage, AK 99507. (907) 344-7863.

May 10—**Consultation With the Alaskan Native Child—Univ. of Wash. Psychiatry Sessions.** Thursday. Anchorage: Contact: Robert F. Kraus, MD, Star Route A, Box 26-B, Anchorage, AK 99507. (907) 344-7863.

MONTANA

January 23-26—**Montana Academy of Family Physicians' Big Sky Medical-Ski Conference.** Tuesday-Friday. Big Sky. Contact: Richard D. Buchanan, MD, P.O. Box 220, Columbia Falls, MT 59912.

January 24-26—**Myocardial Imaging and Radionuclide Analysis of Ventricular Function—Univ. of Wash. Internal Medicine Review Sessions.** Wednesday, Jan. 24, Great Falls. 5-7:30 p.m. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171. Thursday, Jan. 25, Billings. 7-9:30 a.m, Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, Jan. 26, Missoula. 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

February 14-15—**Pediatric Hematology—Univ. of Wash. Pediatrics Sessions.** Wednesday, Feb. 14, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171. Thursday, Feb. 15, Whitefish/Kalispell. Contact: Ronald Miller, MD, 4th and Baker, Whitefish, MT 59937. (406) 862-2515.

February 28-March 2—**Pulmonary Embolism and Asthma. Univ. of Wash. Internal Medicine Review Sessions.** Wednesday, Feb. 28, Great Falls. 5-7:30 p.m. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171. Thursday, March 1, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, Feb. 2, Missoula. 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

March 1-3—**GYN Cancers.** Thursday-Saturday. Big Sky. 12 hrs. Fee: $30. Contact: Western Montana Health Education Council, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

March 2-3—**Montana Cardiologists' Seminar.** Friday-Saturday. Big Sky. Fee: $15. Contact: Western Montana Health Education Council, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

March 9-10—**Drug Therapy: A Review of Basic and Clinical Pharmacology in Practice.** Friday-Saturday. Big Sky. 8 hrs. Fee: $50. Contact: Interhospital Continuing Education Department, Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 14-15—**Pediatric Infectious Diseases—Univ. of Wash. Pediatrics Sessions.** Wednesday, March 14, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171. Thursday, March 15, Whitefish/Kalispell. Contact: Ronald Miller, MD, 4th and Baker, Whitefish, MT 59937. (406) 862-2515.

March 28-30—**An Approach to the Cutaneous Manifestations of Internal Malignancy—Univ. of Wash. Internal Medicine Review Sessions.** Wednesday, March 28, Great Falls. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171. Thursday, March 29, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083. Friday, March 30, Missoula. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

IDAHO

January 16-17—**Pediatric Orthopaedics—Univ. of Wash. Pediatrics Sessions.** Tuesday, Jan. 16, Pocatello. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443. Wednesday,

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: June 6-8, 1979, Shee Atika Lodge, Sitka.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 25-29, 1979, Safari Hotel, Scottsdale.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 9-12, 1979, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 19-23, 1979, the Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 8-12, 1979, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: 1979—date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 4-6, 1979, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 18-20, 1979, Ely Convention Center, Ely.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 2-4, 1979, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Meeting of House of Delegates: April 20-22, 1979, Valley River Inn, Eugene. Annual Scientific Meeting: November 2-4, 1979, OMA Headquarters.

Utah State Medical Association—42 S. 5th East St., Salt Lake City 84102. Annual Meeting: September 11-14, 1979, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 4-7, 1979, Washington Plaza Hotel, Seattle.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: August 28-31, 1979, Jackson Lake Lodge, Moran.

Jan. 17, Boise. 9-10 a.m., Anderson Center. Contact: Thomas Cornwall, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 377-4400.

January 19—**Idaho Chapter, American College of Surgeons' Annual Meeting.** Friday. McCleary Auditorium, Boise. 6 hrs. Contact: Ada County Medical Education Consortium, 190 East Bannock, Boise, ID 83702. (208) 386-2135.

January 27-February 3—**Infectious Diseases in Clinical Practice.** Saturday-Saturday. Sun Valley, Idaho. Contact: Extended Programs in Medical Education, University of California, San Francisco, Rm. 569-U, 3rd and Parnassus Ave., San Francisco, CA 94143. (415) 666-4251.

February 20-21—**Pediatric Hematology—Univ. of Wash. Pediatrics Sessions.** Tuesday, Feb. 20, Pocatello. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443. Wednesday, Feb. 21, Boise. 9-10 a.m., Anderson Center. Contact: Thomas Cornwall, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 377-4400.

February 22-25—**Internal Medicine Residents' Second Annual Winter Retreat.** Thursday-Sunday. Shore Lodge, McCall. Contact: James Hammarsten, MD, Veterans Administration Hospital, 5th and Fort Sts., Boise, ID 83702. (208) 336-5100.

March 2-4—**Ada County and Southwest Idaho Medical Societies' Winter Clinics.** Friday-Sunday. McCall. Hours and fee to be determined. Contact: Ada County Medical Education Consortium, 190 East Bannock, Boise, ID 83702. (208) 386-2135.

March 19—**Infectious Disease—Univ. of Wash. OB-GYN Sessions.** Monday. 12-1 p.m., St. Luke's Hospital, Boise. Contact: David Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391.

March 20-21—**Neonatal Biology. Univ. of Wash. Pediatrics Sessions.** Tuesday, March 20, Pocatello. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443. Wednesday, March 21, Boise. 9-10 a.m., Anderson Center. Contact: Thomas Cornwall, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 377-4400.

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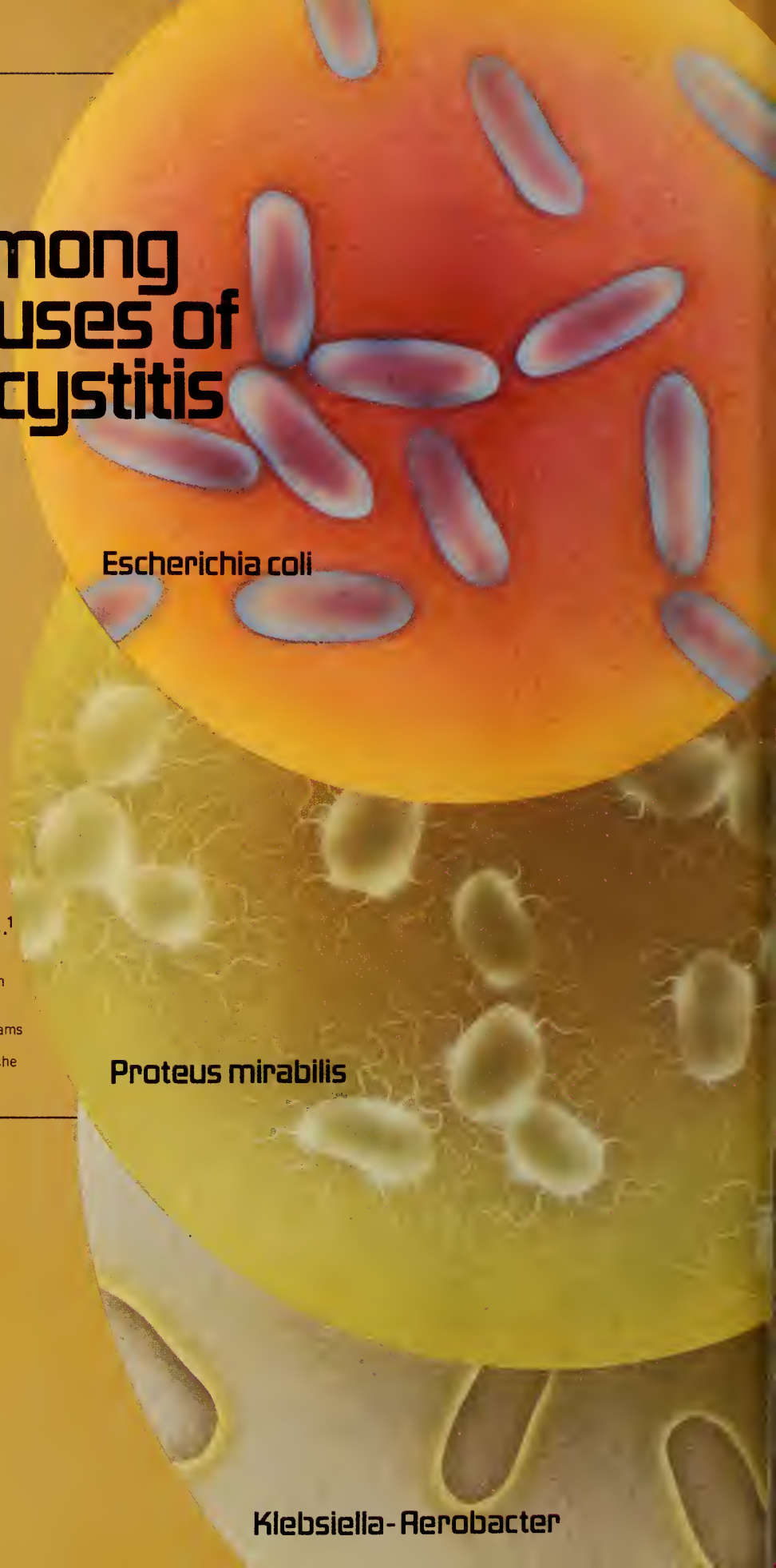
E. coli: first among the causes of acute cystitis



Uncomplicated urinary tract infections, such as acute cystitis, are most frequently caused by serotypes of *E. coli* that are sensitive to the sulfonamides.[1]

References: 1. Johnson JE: Urinary tract infections, chap. 24, in *Clinical Concepts of Infectious Diseases*, edited by Cluff LE and Johnson JE. Baltimore, The Williams & Wilkins Co., 1972, p. 273.
2. Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

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Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

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Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis). *Usual adult dosage:* 2 Gm (2 DS tabs or 4 tabs or 4 teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

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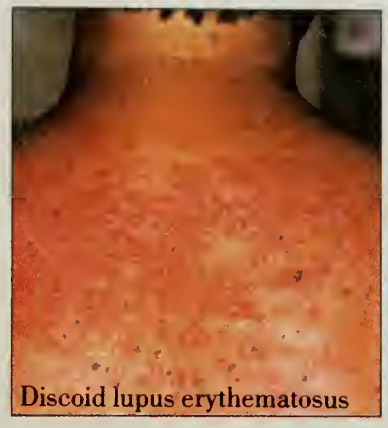
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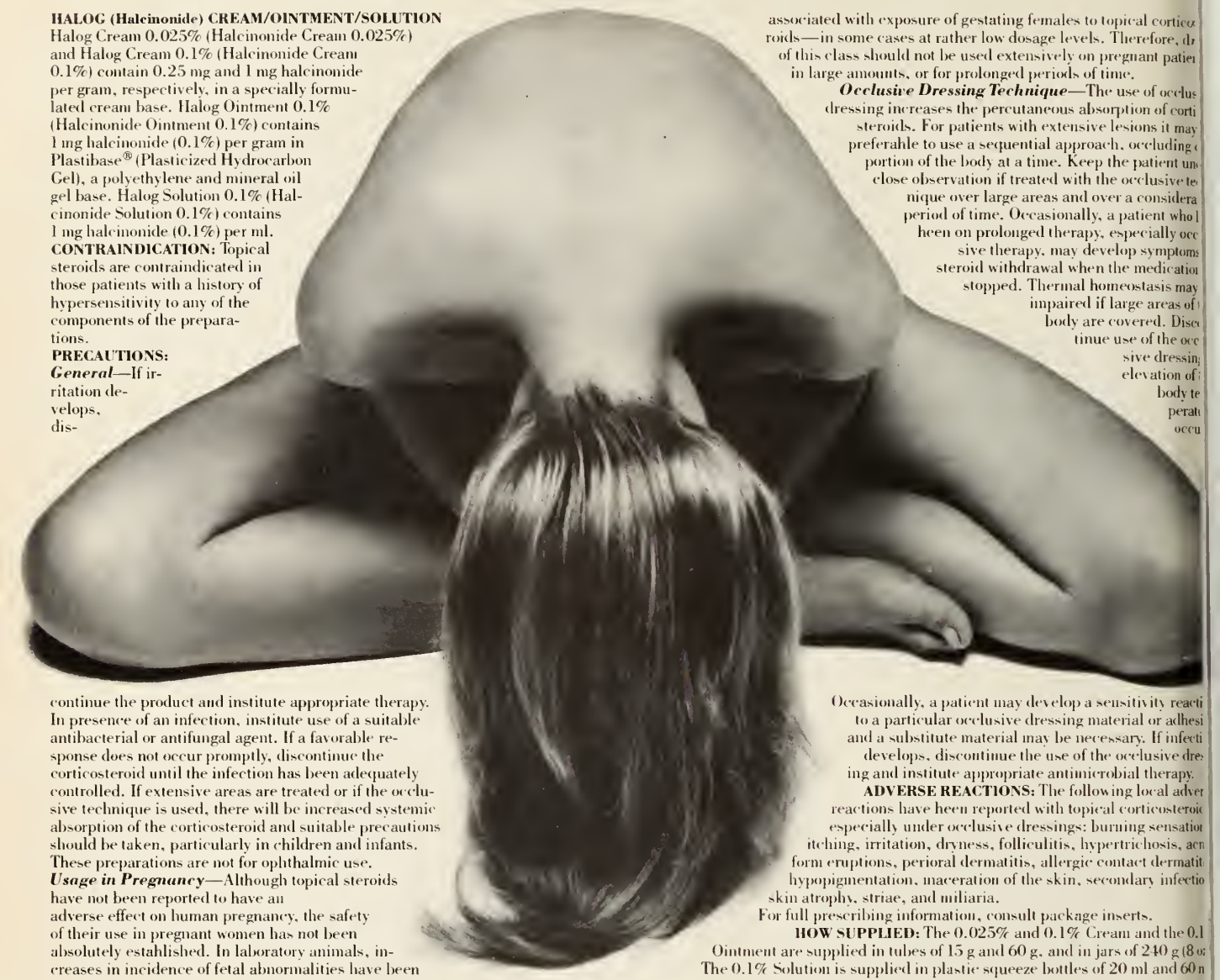

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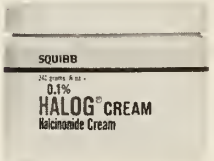

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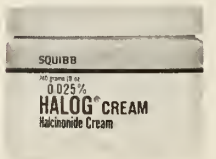

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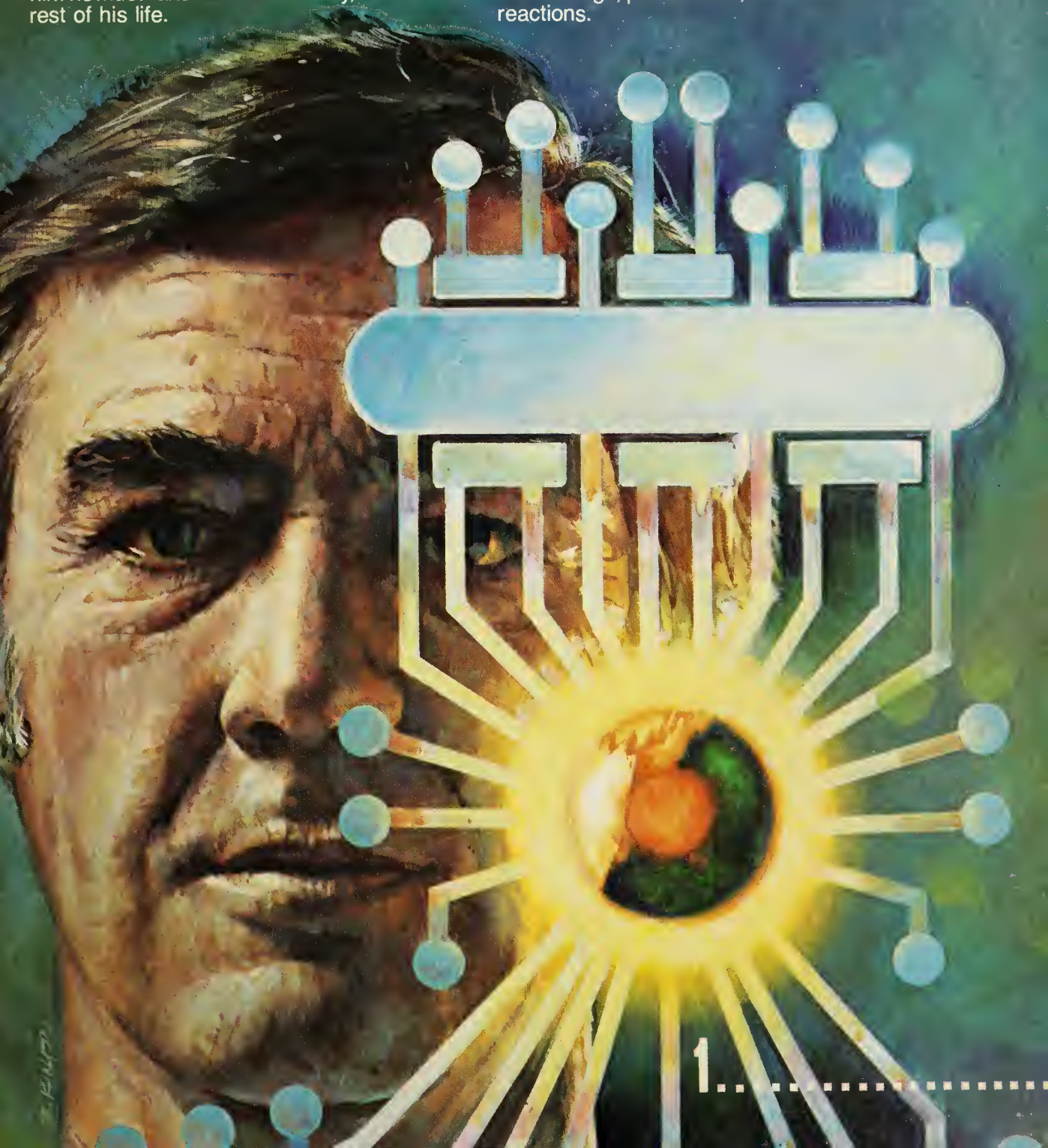

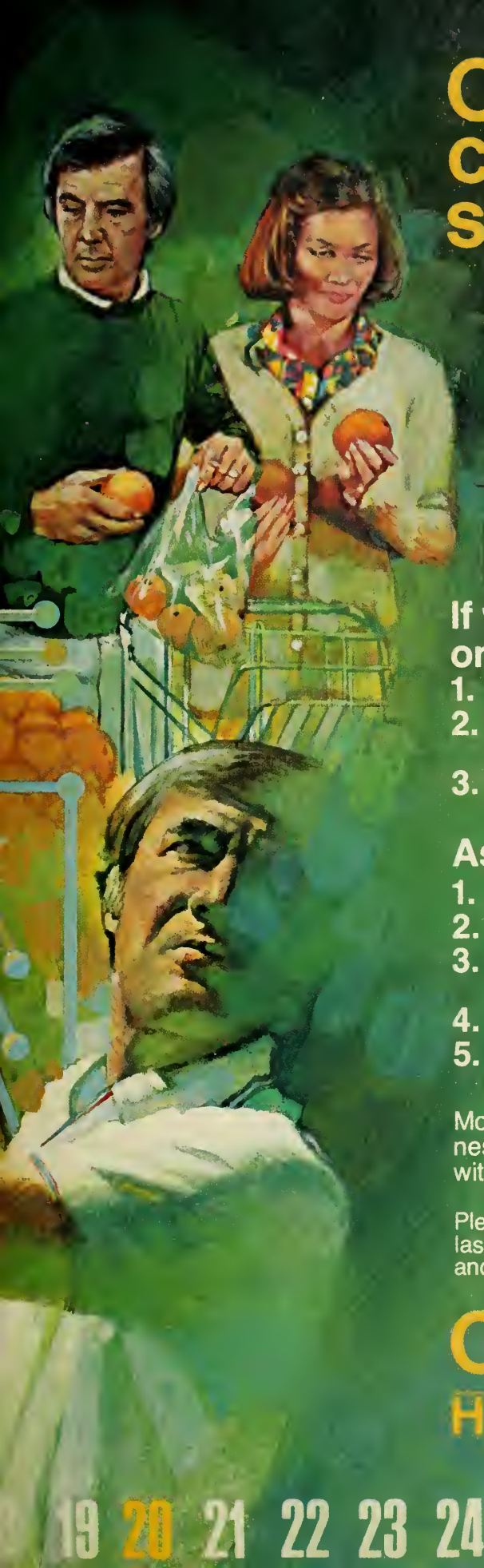

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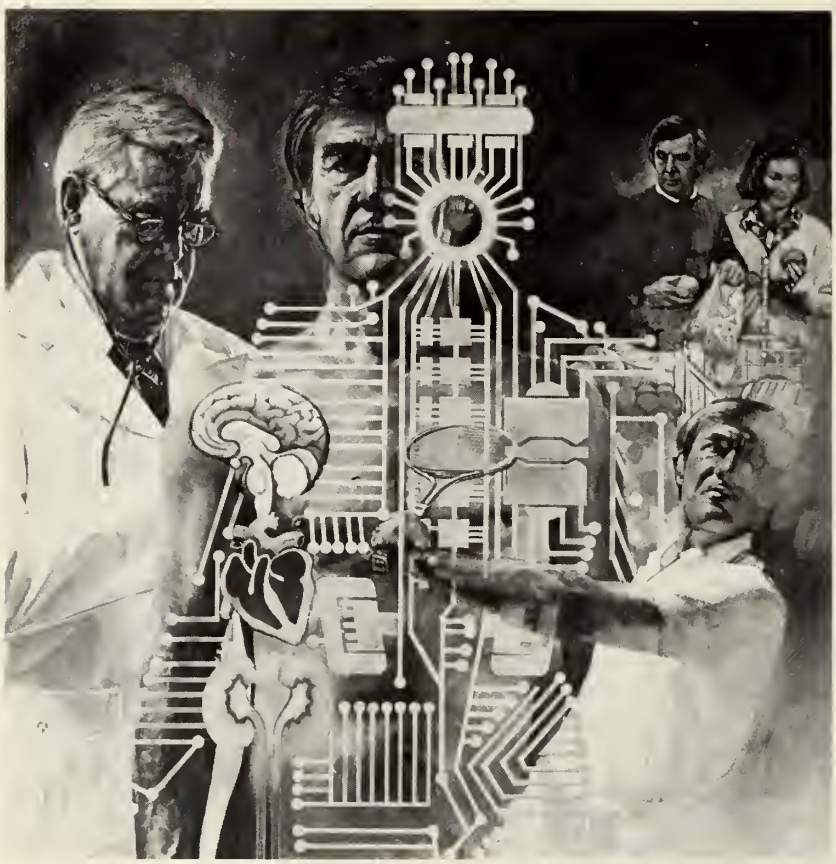

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Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings ii animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus *Usage in Children:* No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive enceph lopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pres sure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any othe agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and menta depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somno lence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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NUTRITION INFORMATION

Portion Size 1 Fluid Ounce (2 Tbs.)	
Servings Per Container	16
Calories	40
Protein	0 grams
Carbohydrate	3 grams
Fat	3 grams
Percent of Calories from Fat	73%
Polyunsaturated Fat	1 gram
Saturated Fat	0 grams
Cholesterol (Δ) (0 mg/100g)	0 mg

In addition to the pint and quart size found in the dairy case of most grocery stores, Mocha Mix is available in 4 ounce and ½ oz. portion packs for hospitals and institutions.

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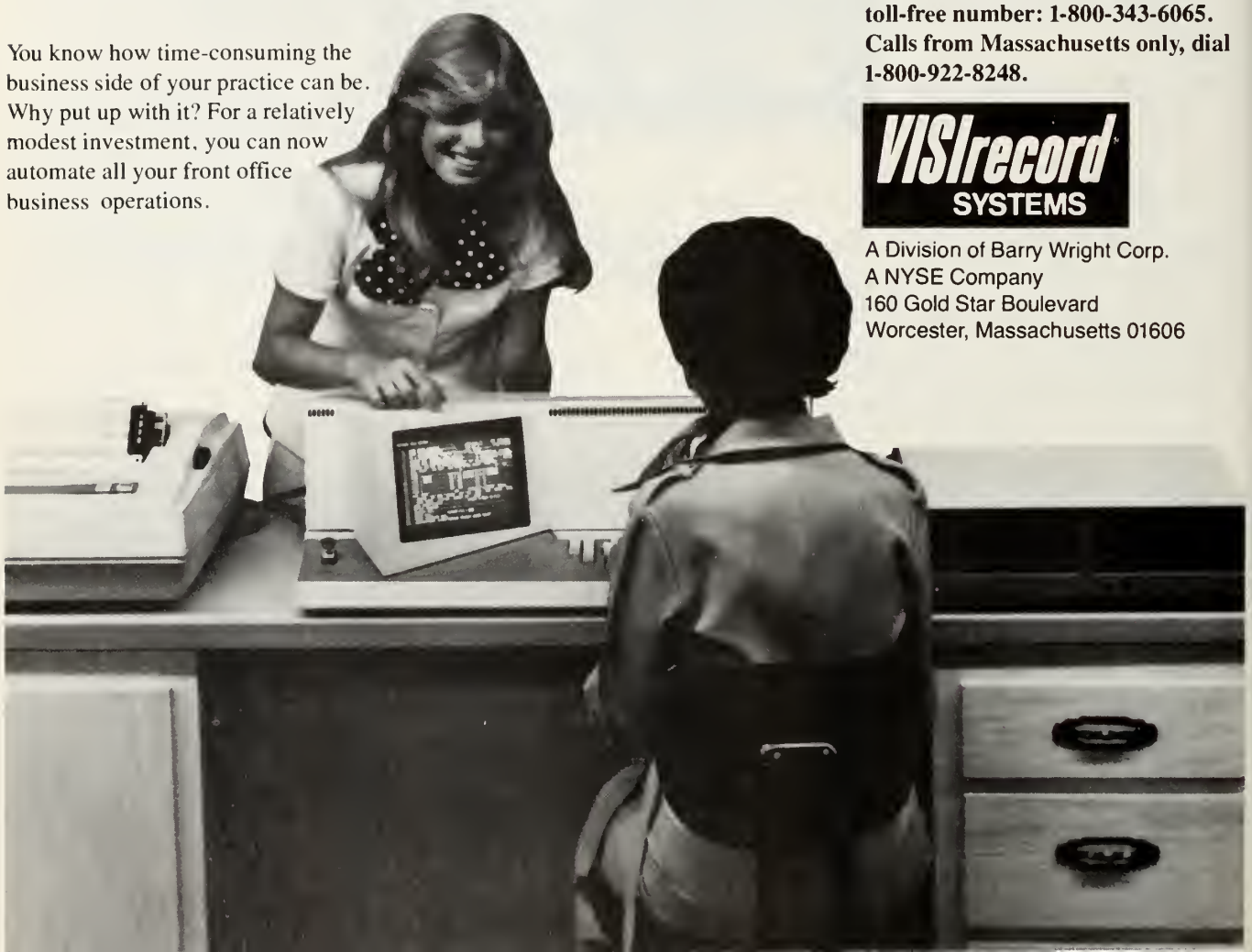

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When you accept no substitutes...

- You ensure that your patient receives exactly that product you have specified on your prescription
- You choose the quality of the product dispensed to your patient
- You can exercise the right to select a product based upon its proven therapeutic performance and to select a manufacturer that stands behind its brand name or generic product
- You can support the kinds of research programs that are vital to new drug discovery and development
- You can help sustain important physician, pharmacist and patient education services supported by innovative, research-oriented firms

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Since October 1974 when Motrin® (ibuprofen) was introduced in the United States, it has been used by more than 6,000,000 patients with rheumatoid arthritis* or osteoarthritis. Rarely has an ethical pharmaceutical product been prescribed for so many patients in so short a time. In addition, more than 450 studies presenting new data related to Motrin have been published.

The 6,000,000 patients already treated with Motrin is an objective measure of physicians' confidence in the ability of Motrin to relieve the pain and inflammation associated with rheumatoid arthritis and osteoarthritis.

So it is not surprising that in this short period Motrin has become the most frequently prescribed alternative to aspirin. Motrin relieves joint pain and inflammation as effectively as indomethacin or aspirin, but causes significantly fewer CNS and milder GI reactions. However, gastrointestinal bleeding, sometimes severe, has been associated with Motrin, aspirin, indomethacin, and other nonsteroidal antiarthritic agents.

*The safety and effectiveness of Motrin have not been established in patients with Functional Class IV rheumatoid arthritis (incapacitated, largely or wholly bedridden, or confined to wheelchair; little or no self-care).

Motrin 400 mg TABLETS
ibuprofen, Upjohn

The confidence that comes from experience—
one more reason to prescribe Motrin.

Please turn page for a brief summary of prescribing information.

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001

The confidence that comes from experience—
one more reason to prescribe

Motrin 400 mg TABLETS
ibuprofen, Upjohn

Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin* used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin (ibuprofen) is gastrointestinal (4% to 16%). This includes nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness*, headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

Incidence: Unmarked 1% to 3%; *3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Suggested dosage is 300 or 400 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day.

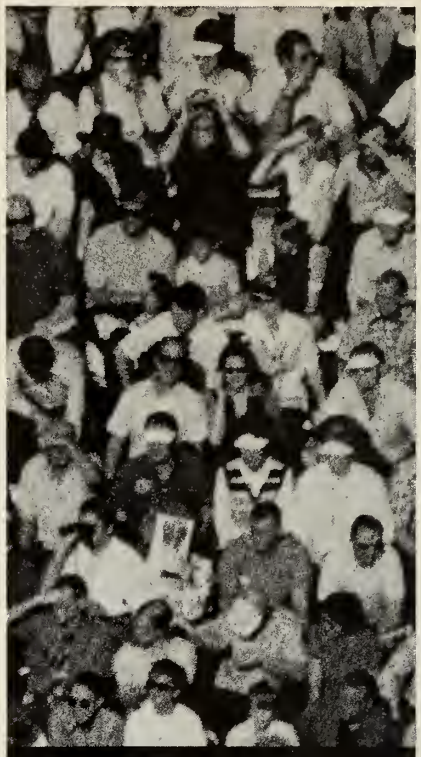
How Supplied

Motrin Tablets, 300 mg (white)	
Bottles of 60	NDC 0009-0733-01
Bottles of 500	NDC 0009-0733-02
Motrin Tablets, 400 mg (orange)	
Bottles of 60	NDC 0009-0750-01
Bottles of 500	NDC 0009-0750-02
Unit-dose package of 100	NDC 0009-0750-06
Unit of Use bottles of 120	NDC 0009-0750-26

Caution: Federal law prohibits dispensing without prescription.

NIM-3

Upjohn The Upjohn Company



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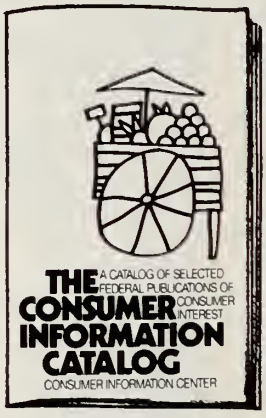
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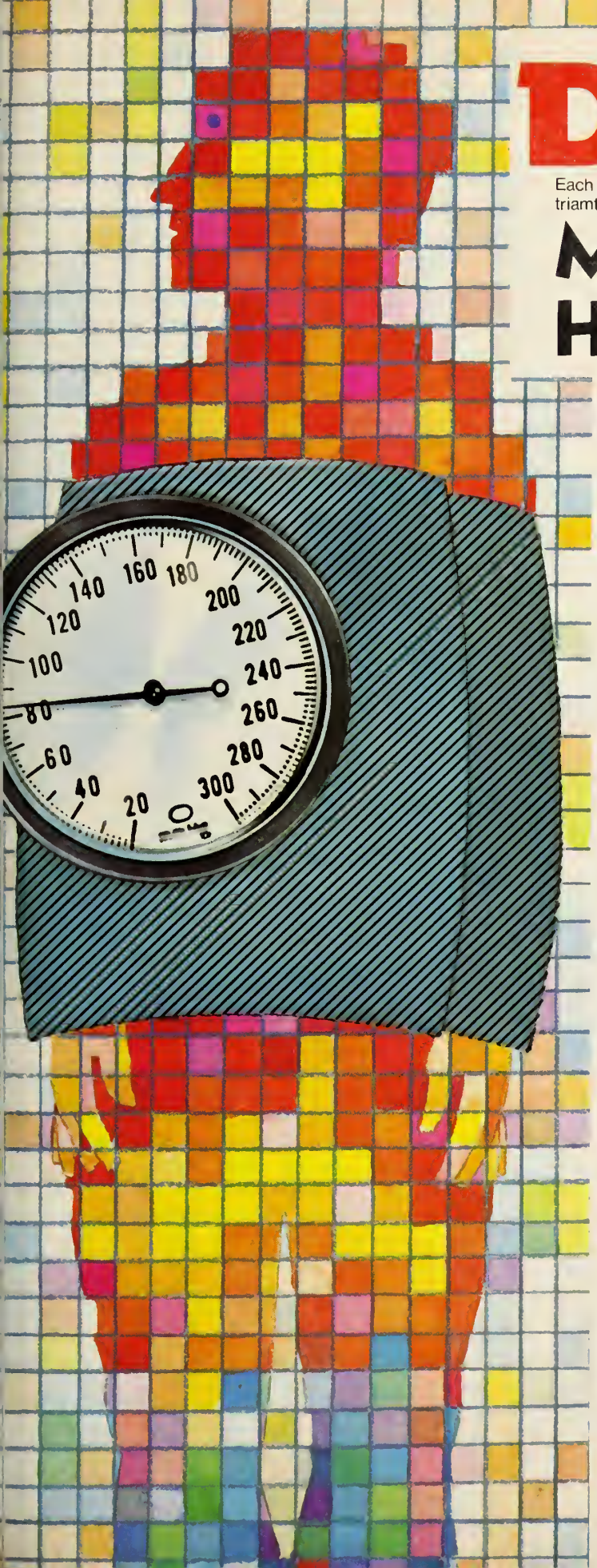

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Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **Warning**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K+ frequently; both can cause K+ retention and elevated serum K+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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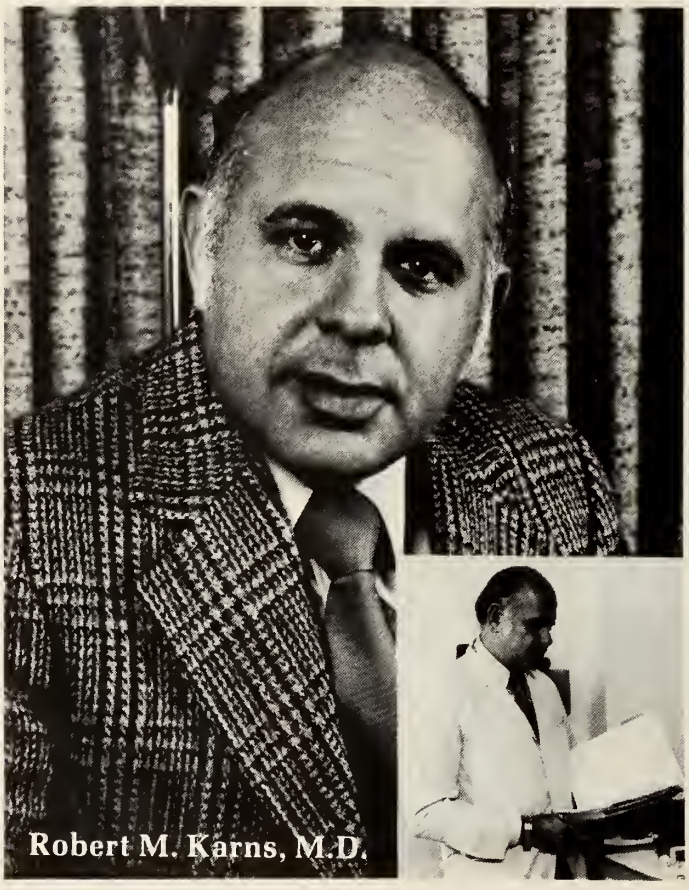

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Warnings: Do not administer more frequently than every 6 hours, or within 12 hours after rectal dose of any preparation containing theophylline or aminophylline. Do not give other compounds containing xanthine derivatives concurrently.

Precautions: Use with caution in patients with cardiac disease, hepatic or renal impairment. Concurrent administration with certain antibiotics, i.e., clindamycin, erythromycin, troleandomycin, may result in higher serum levels of theophylline. Plasma prothrombin and factor V may increase, but any clinical effect is likely to be small. Metabolites of guaifenesin may contribute to increased urinary 5-hydroxyindoleacetic acid readings when determined with nitrosonaphthol reagent. Safe use in pregnancy has not been established. Use in case of pregnancy only when clearly needed.

Adverse Reactions: Theophylline may exert some stimulating effect on the central nervous system. Its administration may cause local irritation of the gastric mucosa with possible gastric discomfort, nausea, and vomiting. The frequency of adverse reactions is related to the serum theophylline level and is not usually a problem at serum theophylline levels below 20 mcg/ml.

How Supplied: Capsules in bottles of 100 and 1000 and unit-dose packs of 100; Liquid in bottles of 1 pint and 1 gallon.

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Clinical Nutrition Is a Medical Specialty

ROBERT H. HERMAN, MD
LOUIS HAGLER, MD
San Francisco

FEATURED in this issue of THE WESTERN JOURNAL OF MEDICINE is a symposium on clinical nutrition. It should be evident from the content of the symposium that clinical nutrition is a medical specialty. Clinical nutrition deals with the relation between disease and nutrition. Dietary components can cause acute and chronic illness when deficient, when present in excess or when present in "normal" amounts in susceptible persons who have genetic disease or metabolic conditions, or who are taking certain drugs. Maintenance of a patient's nutritional status is a time-honored approach to the treatment of disease. With the advent of techniques for total parenteral nutrition an increased degree of versatility has been attained for the treatment of conditions which until now had not been amenable to therapy.

Despite the recognition that dietary components or their absence can cause illness, that chronically ill patients often are malnourished and that nutritional therapy is technically possible in conditions in which it had been impossible, there still is reluctance by some to accept clinical nutrition as a medical specialty. Instead nutrition is fragmented among other medical specialties where it is used only within the context of that specialty without regard for clinical nutrition as an entity.

Part of the problem is due to the early spectacular results in nutrition research and the consequent prevention of nutritional deficiencies. Beginning in the early 1900's vitamins have been discovered and their mechanisms of action (with a few exceptions) have been adduced. No longer need we fear the specter of vitamin deficiency diseases. The requirements for proteins, essential amino and fatty acids, vitamins and calories have been determined. More recently the requirements for trace minerals have been determined. We can prevent nutritional deficiency diseases, treat them specifically when they do occur, and effect a cure. Nutritional deficiency diseases no longer occur in epidemic form in the United States. The malnutrition that does occur is a consequence of chronic illness, self-neglect, ignorance, or is seen in conjunction with alcoholism or drug addiction. In fact, obesity rather than malnutrition is a major nutritional illness in the United States. The prevention of nutritional deficiency diseases has been so successful and has been so identified with clinical nutrition that clinical nutrition has been relegated to the medical background.

In addition, these past accomplishments of clinical nutrition have been overshadowed largely by recent developments in molecular biology, cardiac catheterization, electronic monitoring devices and techniques, surgical transplantation, chemotherapeutic techniques, computerized axial tomography, newer noninvasive diagnostic techniques, radioisotopic methods of diagnosis and treatment, advances in endocrinology and so on; in short, the great achievements of modern medicine. These are great advances of far-reaching consequences for the future. Yet, by a number of measures—prevention of disease, effectiveness of treatment, relative cost—these latest advances cannot match the past successes of clinical nutrition. No matter how intellectually satisfying, exciting and impressive (and they are impressive) are the recent discoveries in molecular biology (such as DNA biosynthesis, nucleosome structure

Refer to: Herman RH, Hagler L: Clinical nutrition is a medical specialty—Introductory Remarks (Clinical Nutrition Symposium). West J Med 130:93-94, Feb 1979

From Department of Medicine, Letterman Army Institute of Research, San Francisco.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Reprint requests to: Robert H. Herman, MD, Chief, Dept. of Medicine, Letterman Army Institute of Research, Presidio of San Francisco, CA 94129

within chromatin, gene inserts, protein biosynthesis, restriction enzymes, cloning techniques) the immediate application to clinical medicine is limited and costly and in general disease prevenion is not yet possible. The newer diagnostic and therapeutic approaches are also limited in application and are expensive. Whenever the fabric of society breaks down as a consequence of a natural catastrophe (flood, drought, storm, earthquake or the like) or some social upheaval (such as war, revolution or economic collapse) the twin evils of nutritional deficiency and infection reappear indicating how vulnerable we are to these age-old afflictions of man. Even in the case of infectious diseases where there have been great triumphs in disease prevention with vaccines and treatment with antibiotics there has been a gradual emergence of antibiotic resistant organisms.

Research in clinical nutrition has not stood still. Advances have been made in understanding the mechanisms of action of vitamins A, D, E and K. The biochemical functions of selenium and zinc have been discovered. The role of dietary fiber in the cause and management of disease is being studied intensively. The relationship between dietary lipid and coronary artery disease is gradually yielding to constant inquiry. The role of nutrients as a cause of illness is now better understood. The techniques of total parenteral nutrition have not only enabled us to provide nutritional support and therapy when enteral feeding is impossible but has forced us to consider what are the total nutritional requirements of man.

Major national health problems still exist. We are faced with the widespread occurrence of atherosclerosis in its various manifestations, obesity, diabetes, hypertension, osteoporosis, cancer, alcoholism and its myriad complications, and drug addiction among others. The possible or probable nutritional involvement in coronary artery disease, obesity, diabetes, hypertension, osteoporosis and alcoholism has been investigated extensively. Even the role of dietary components in the pathogenesis of neoplastic disease is under consideration (nitrates, nitrites and nitrosamines, and aflatoxins are examples). How much more effective (in time, effort, money and reduction of distress for the patient) would it be to prevent coronary artery disease and cancer by alterations in diet than to apply diagnostic studies, chronic management or heroic treatment? But, in order to explore the clinical nutritional aspects of these chronic, disabling and lethal diseases we must first recognize clinical nutrition as a medical specialty in its own right.

We hope that this symposium on clinical nutrition provides knowledge of some of the recent developments in clinical nutrition and engenders a deeper appreciation of clinical nutrition as a medical specialty.

Food Intolerance in Humans

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IT IS WELL KNOWN that deficient intake of protein, calories, vitamins or minerals leads to a variety of nutritional disorders. It is known that food contaminated with toxic materials or microorganisms may cause illness if consumed. It is also known that certain foods naturally contain nonnutrient poisonous substances that may cause illness and in some cases, death. Nevertheless, it is not generally realized that the nutrient components of food, in themselves, may be toxic for certain people, causing illness or aggravating preexisting illness.

Food intolerance may be defined as any illness or biochemical or metabolic abnormality that is causally connected to the ingestion of any food or dietary component. An illness that is causally connected to a *nonnutritive* dietary component may be referred to as food poisoning or food toxicity. The term food intolerance is usually applied to illness resulting from the ingestion of substances that have *nutritive* value such as carbohydrates, lipids, proteins and amino acids. Logically speaking, vitamins, minerals, water and oxygen are nutrients and under certain circumstances may cause illness. Water and oxygen are not usually thought of as food although there is no question that they are vital nutrients. In addition, one should add purines to the list of nutrients capable of aggravating preexisting disease, although they are dispensible nutrients.

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There may be an obvious connection between food ingestion and the production of acute illness or a less obvious connection so that a patient may fail to recognize the relationship between his disease and the offending dietary component.

Under special circumstances certain combinations or amounts of food substances may cause illness in otherwise healthy persons. For example, fasting followed by refeeding may result in gastrointestinal symptoms and edema due to sodium retention. This is an example of food intolerance which can occur in otherwise healthy persons. Many illnesses may cause anorexia and may lead to nausea and vomiting when eating is attempted. This type of food intolerance may be considered to be a secondary type since the food is not toxic but the illness has so altered the normal physiology that the patient becomes intolerant to many types of foods. Primary disorders of smell and taste may cause the patient to reject food as unpalatable. Psychological disturbances, cultural habits, personal preferences, religious edicts and the like may render certain foods unacceptable to certain persons or groups of people. This is a difficult area to study but a most important one. Food manufacturers especially are aware of these psychological problems and attempt to engender psychological acceptability for their products in consumers.

We must also consider foods that are toxic for some people for reasons that are not clear. Often allergy or psychological aversion is invoked to explain the sensitivity or distaste a person has for a particular food. Although both food allergies and psychological aversions are well known to exist, these are often not adequate explanations for the illnesses that follow the ingestion of cer-

tain foods. Therefore, there are many foods that are toxic for some people for unknown reasons.

In this paper we shall consider only those food intolerances that are related to nutrients but not those that are caused by nonnutrient substances that are endogenously produced within food or that are exogenously produced and enter somehow into the food.

Definitions

The following definitions are used:

- A chemical is any substance with a defined structure and specific properties.
- A metabolite is any chemical that is transformed into one or more derivatives by the metabolic processes of the body. Physiological and nonphysiological substances that are transformed or metabolized by the body are metabolites. Certain substances may be absorbed and retained or excreted in unchanged form (or both). Such materials would not be considered to be metabolites and may be nontoxic unless they occupy space thereby interfering with normal function. Such substances although not metabolized may bind to proteins or cell membranes or may be transported through cell membranes. In some cases chemically inert radioactive substances are stored by tissues and prove to be toxic because of their radioactivity. Certain substances are not absorbed or altered and pass through the gastrointestinal tract unchanged while others are metabolized only by the gastrointestinal flora.
- A nutrient is any chemical that is utilized by the body to produce energy or a cellular structure either directly or indirectly. Although water and oxygen are essential nutrients the toxic effects of each will not be considered.
- An essential nutrient is one that is not synthesized at all or only partially by the metabolic processes and leads to recognizable illness when totally excluded from the diet.
- A nonessential nutrient is one that can be synthesized by the metabolic processes of the body but can also be supplied by the diet. Total exclusion of a nonessential nutrient from the diet does not lead to any recognizable illness. Both essential and nonessential nutrients are metabolites.
- Food is any nutrient or mixture of nutrients and other chemicals that is eaten and processed in the digestive system. This processing includes mastication, swallowing, digestion, absorption, intermediary metabolism and excretion. Food may be relatively simple and pure chemically (such as sodium chloride or sucrose) or extremely complex, being composed of a great variety of substances all of which may not be known (such as chocolate layer cake, milk, eggs or oranges). In complex foods the amount of any given component may vary at different times. Food, in addition to one or more nutrients, may contain metabolites, nondigestible substances, endogenously produced substances (such as flavor and aroma-producing substances, caffeine and other drug-like agents) and exogenously added substances (coloring agents, emulsifiers, antibiotics, antioxidants and so forth). One must distinguish between nutrients and foods. Not all nutrients are considered to be foods—water and oxygen, for example.
- Pseudofoods are certain substances that are considered to be food items in spite of the fact that they contain few if any nutrients. These substances may contain many chemicals some of which have potent physiological effects and may be considered to be drugs. In this category belong coffee, tea, chocolate, spices and herbs.
- A drug or medication is any chemical that is administered to a patient to produce a therapeutic effect. Drugs may be either physiological or nonphysiological substances either derived from natural sources or from synthetic processes. Drugs may be administered in nonphysiological doses and through nonphysiological routes.
- Ethanol is a simple alcohol which in smaller amounts is a nonessential nutrient providing calories (7.07 kcal per gram) and in larger amounts is a drug that produces its well-known intoxicating effects acutely and pathological effects after long-term use. Because of the tax laws its use is regulated by the United States Department of the Treasury rather than the Food and Drug Administration and the toxic effects are studied by the National Institute on Alcohol Abuse and Alcoholism which is part of the Alcohol, Drug Abuse, and Mental Health Administration of the United States Public Health Service.

Classification of Food Intolerance

Food intolerance is classified as shown in Table 1. Many nonnutrient substances can cause a large variety of illnesses. Substances not part of a particular food may enter into the food while in its natural state. Substances may be added to foods during processing or may enter into foods from

TABLE 1.—*Classification of Food Intolerance*

Nonnutrient substances
Exogenous substances
Endogenous substances
Nutrient substances
Carbohydrates
Proteins and amino acids
Lipids
Minerals
Vitamins
Purines
Water
Oxygen
Multiple food intolerances
Idiopathic food intolerance

bacteria, molds or fungi growing on the food. Chemical substances or microorganisms may contaminate food. An animal may eat a plant or another organism and thereby acquire a toxic substance. These are exogenous nonnutrient substances. On the other hand, a food source may produce substances by virtue of its own metabolism that are toxic when ingested. Such substances may be toxic for all persons or may be toxic only for some persons by virtue of some metabolic condition or the use of a particular drug. These substances are endogenous nonnutrient substances. It is not possible in this paper to consider the food intolerances caused by nonnutrient substances because of the large number of such substances and their diverse effects.

Food intolerance is caused by nutrient substances. Although purines, water and oxygen can cause illness in the appropriate circumstances, we shall consider mainly those disorders related to carbohydrates, amino acids and proteins, lipids, minerals and vitamins.

There are numerous medical conditions in which many different foods cause symptoms. These can be considered in the category of multiple food intolerances. The symptoms may be either a nonspecific portion or a dominant aspect of a particular disease. Anorexia as part of an acute illness is well known but the mechanism is often obscure. Patients may desire little if any food and attempts to eat may lead to nausea and vomiting. On the other hand, in anorexia nervosa the patients may eat small amounts of food but not enough to maintain normal weight. In some instances a person may be intolerant of a great variety of foods. A patient with anosmia or dysgeusia may be poorly tolerant of all foods because of the disturbance of smell and taste. Here the reason for food intolerance is apparent although

TABLE 2.—*Carbohydrate-Induced Food Intolerance*

Glucose-galactose intolerance due to glucose-galactose malabsorption
Lactose intolerance due to lactase deficiency
Sucrose-starch intolerance due to sucrase-isomaltase deficiency
Sucrose-fructose intolerance (hereditary fructose intolerance) due to fructose-1-phosphate aldolase deficiency
Sucrose-fructose-glycerol intolerance due to fructose diphosphatase deficiency
Galactose intolerance
Galactosemia due to uridyl transferase deficiency
Cataracts due to galactokinase deficiency
Galactose intolerance after ethanol ingestion
Trehalose intolerance due to trehalase deficiency
Starch intolerance due to α-amylase deficiency
Carbohydrate intolerance
Reactive hypoglycemia
Hyperlipoproteinemia (type IV)
Glucose intolerance and hyperinsulinemia
Obesity
Precipitation of paralysis in familial hypokalemic periodic paralysis especially after exercise
Gastrointestinal maladaption syndrome related to failure of jejunal glycolytic enzyme adaptation to dietary carbohydrate
Primary
Secondary
Postoperative dumping syndrome
Lactic acidosis due to pyruvate dehydrogenase deficiency
Dental caries related to sucrose and Streptococcus mutans
Raffinose-stachyose-verbascose intolerance due to indigestibility

the basic disorder of smell and taste is usually unknown. In this regard the problem of anorexia and zinc deficiency is considered elsewhere in this symposium.

A final category of food intolerance is the idiopathic variety. Usually the person becomes ill after eating a particular food. The offending substance may not be known. Allergic or idiosyncratic mechanisms may be invoked but such semantic explanations are not very helpful. This category of food intolerance merely serves to alert the investigator that a particular food can cause illness and, therefore, is a prime target for investigation.

Carbohydrate-Induced Food Intolerance

Table 2 lists disorders related to various carbohydrates. *Glucose-galactose intolerance* occurs infrequently in infants.[1,2] Because of the inability to absorb these sugars an osmotic diarrhea occurs. It is presumed that there is a defect in the glucose-galactose carrier protein in the small intestinal mucosal epithelial cells.[3] Renal glycosuria also is

seen in this condition presumably because of a similar carrier protein defect. The condition may be treated by restricting glucose and galactose in the diet and using fructose as a source of dietary carbohydrate.[4-7]

Lactose intolerance is most common.[8-15] Most people in the world are lactase deficient. Therefore, milk intolerance is not uncommon because of the lack of the jejunal brush border enzyme, lactase. In lactase deficiency the lactose of milk cannot be hydrolyzed and an osmotic diarrhea occurs together with fermentation of the lactose by intestinal microorganisms. Lactase deficiency may occur at an early age or may occur at variable ages in different persons. Lactose intolerance, therefore, may be present at birth or may occur late in life. Treatment requires the avoidance of lactose by restricting dietary milk and milk-containing products. Lactose intolerance should not be confused with milk allergy which is related to milk proteins. This will be discussed in the section on amino acid-induced and protein-induced food intolerance.

Sucrose-starch intolerance is a rare entity. This is caused by a deficiency of two jejunal brush border enzyme activities, sucrase and isomaltase.[16,17] Each of the enzyme activities is contained at a different site within one polypeptide molecule[18] which serves as a multifunctional enzyme.[19] A deficiency of these enzyme activities leads to failure of hydrolysis of sucrose and the isomaltose derived from the digestion of starch. The unhydrolyzed sucrose and isomaltose cause an osmotic diarrhea and are also fermented by intestinal bacteria. Therapy requires the restriction of dietary sucrose and starch. Fructose also may be used to treat this condition[20] because fructose can increase the activity of sucrase and isomaltase.[21] In one patient with sucrase-isomaltase deficiency given dietary fructose the enzymes increased in activity, although not to normal levels, and increased the tolerance of the patient to dietary sucrose.[20]

Sucrose-fructose intolerance occurs in the disease hereditary fructose intolerance.[22] In this condition the enzyme fructose-1-phosphate aldolase is lacking in various tissues, notably the liver. Ingestion of sucrose or fructose leads to the accumulation of fructose-1-phosphate in the liver and other tissues and results in hypoglycemia.[23] This may be so severe that shock and death may occur. Treatment involves restricting dietary sucrose and fructose. It is possible to increase the activity of fructose-1-phosphate aldolase by the oral administration of folic acid in pharmacological doses.[24] The enzyme activity increases to higher levels although it does not reach normal values. Folic acid has been found to increase the activities of glycolytic enzymes of the jejunum and liver although the mechanism of action is not clear.[25,26] Fructose-1,6-diphosphate aldolase activity is diminished in this condition although there is sufficient activity for normal function.[22] Both fructose-1-phosphate aldolase and fructose-1,6-diphosphate aldolase activities are contained within a single polypeptide chain although each activity resides in a different region.[27] This single polypeptide is another example of a multifunctional enzyme.[19] It is of interest that persons with hereditary fructose intolerance rarely have dental caries because they quickly learn to avoid dietary sucrose strictly.[22]

Sucrose-fructose-glycerol intolerance occurs in persons with fructosediphosphatase deficiency.[28-30] This enzyme is critical for the function of the gluconeogenetic pathway in the liver.[30] A deficiency of this enzyme may result in chronic hypoglycemia,[29] ketotic hypoglycemia[28] or in a rare case, reactive hypoglycemia.[30] Hypoglycemia can be provoked by sucrose, fructose, glycerol, ethanol, a ketotic diet and fasting (such as may occur in an anorectic illness). Treatment involves restriction of sucrose, fructose and glycerol, and frequent feedings with glucose in the chronic hypoglycemic form of the disease.[28-30] Folic acid may increase the activity of fructose-diphosphatase and thereby improve the blood glucose levels in the chronic hypoglycemia form of the disease[29] and may protect those patients with the milder forms of the disease.[28,30]

Galactose is toxic in galactosemia in which the enzyme uridyl transferase in the galactose metabolic pathway is deficient.[31,32] The lactose of milk, when hydrolyzed, yields glucose and galactose. Galactose in the diet is provided almost exclusively from milk and milk products. Ingestion of galactose results in the accumulation of galactose-1-phosphate in the tissues of several organs including the liver, kidney and lens of the eye.[31,32] Continued accumulation causes hypoglycemia, cataracts, mental retardation, growth retardation, and hepatic and renal damage. Ultimately the condition ends fatally.[31] Treatment consists of galactose restriction by the elimination of milk and milk-containing products from the diet.[31,32] In addition to the "classical" form of the galac-

tose-1-phosphate uridyl transferase variant which is responsible for the first recognized severe form of galactosemia, at least five additional variant forms of the enzyme have been described.[33] Two of the variants (Duarte and Los Angeles) cause no clinical manifestations in the homozygous form, one may cause mild symptoms ("Negro"), and three are associated with severe symptoms of galactosemia (classical, Indiana, Rennes). Galactose may cause blurred vision in normal persons when given in amounts that greatly exceed the usual dietary levels. Administration of 450 grams of galactose per day to normal persons caused blurred vision due to edema of the lens.

Ingestion of galactose by persons with *galactokinase deficiency* results in cataracts but none of the other clinical manifestations seen in galactosemia.[34-36] Galactokinase deficiency is also treated by eliminating milk and milk-containing products from the diet. The ingestion of ethanol impairs the activity of an enzyme, 4′-epimerase,[37] which is another enzyme in the galactose metabolic pathway. Therefore, galactose tolerance becomes abnormal if galactose is administered after the consumption of ethanol.[38,39] In animals a combination of ethanol and galactose feeding is more lethal than either alone.[40]

Vomiting and diarrhea have been reported in one family after they ate mushrooms.[41] The symptoms disappeared in one day. The mushroom intolerance was secondary to the *deficiency of jejunal trehalase,* a brush-border disaccharidase. Mushrooms contain a disaccharide, trehalose, which cannot be hydrolyzed in trehalase deficiency and, therefore, causes an osmotic diarrhea.

Starch intolerance has been described in patients with a selective deficiency of pancreatic α-amylase.[42,43] Diarrhea occurred as a consequence of the fermentation by gastrointestinal flora of undigested starch. It was suggested[43] that there was late maturation of the biosynthetic mechanism for the pancreatic amylase. The exact molecular nature of the amylase deficiency is unknown. Treatment consisted of eliminating starch from the diet.

A high carbohydrate diet, in general, may be related to a number of medical problems. A high carbohydrate diet may be involved with reactive hypoglycemia.[44] Reactive hypoglycemia can be classified as diabetic, alimentary, hormonal (hypothyroidism, Addison disease), or idiopathic in type.[44] In a rare case fructosediphosphatase deficiency may cause "idiopathic" reactive hypoglycemia.[30] In many patients with the so-called type IV hyperlipoproteinemia, panhyperlipemia may develop as a consequence of a high carbohydrate diet.[45-51] The panhyperlipemia may decrease when their high carbohydrate diet is restricted. Maturity onset diabetes usually is associated with a high carbohydrate diet. Early, an abnormal glucose tolerance and hyperinsulinemia occur.[52-57] Restriction of the high carbohydrate diet may bring the glucose tolerance and serum insulin levels to normal.[53-55] Obesity is very common in maturity-onset diabetes.[52-57] Obesity, of course, is a consequence of long-term high carbohydrate ingestion, which generally is the source of the excess calories that gave rise to the obesity.[58] This problem is considered in more detail elsewhere in this symposium. A high carbohydrate intake, especially when combined with exercise, may precipitate paralysis in familial hypokalemic periodic paralysis.[59]

The *feeding of glucose and fructose to normal persons* results in an increase in the activities of various jejunal epithelial glycolytic enzymes and a decrease in the activity of fructosediphosphatase.[26,60] There are patients who have chronic intermittent diarrhea or a dumping-like syndrome,[61] or both, with no known cause. Careful and extensive study in these patients has failed to show any intestinal lesion or any other disease. The administration of glucose and fructose to these patients provokes their symptoms. Small intestinal tissue obtained by peroral biopsy[62] for analysis of glycolytic enzyme activities has shown failure of the normal adaptive enzyme response.[61] In many of these patients the condition often improves when they receive a low carbohydrate diet.[61] The nature of this type of carbohydrate intolerance is unknown but has been termed the gastrointestinal maladaptation syndrome.

In patients with histological abnormalities of the small intestine the normal adaptive response of the glycolytic enzymes may be lost. Successful treatment of the small intestinal disease results in the return of the normal adaptive response. This sequence of events has been found to occur in *tropical sprue.*

Persons who have been starving or have been subsisting on a *low carbohydrate diet* show a decrease in the activities of their jejunal glycolytic enzymes. Acute administration of carbohydrate in the form of glucose may cause diarrhea or other gastrointestinal symptoms.

Carbohydrate feeding after gastrointestinal re-

section may lead to the so-called *dumping syndrome*.[63,64] The mechanism of the dumping syndrome is unclear.

In patients with the rare disease *pyruvate dehydrogenase deficiency,* an increased carbohydrate intake may cause lactic acidosis.[65-67] In such patients the lactic acidosis can be ameliorated by restricting dietary carbohydrate.

The occurrence of *dental caries* is a very common condition which is related to the ingestion of refined sugar.[68-71] A gelatinous material, plaque, forms on teeth and becomes colonized by bacteria, mainly Gram-positive streptococci. Plaque is composed of oral microorganisms and an extracellular matrix of bacterial polysaccharides, leukocytes, salivary glycoproteins, water and epithelial cell remnants.[69,70] Sugars, especially sucrose, promote the formation of plaque.[69] Sucrose promotes the formation of dextrans by and the colonization of plaque by Streptococcus mutans which is considered to be a primary microbial agent of plaque.[69] The acid produced by the plaque bacteria erodes the teeth and forms dental caries.[69] Bacterial and leukocytic enzymes may also degrade the organic components of enamel and dentine.[69,70] In those societies in which refined sugar (sucrose) is not used dental caries rarely occur.[68] Dental caries cannot be induced in germ-free animals no matter how cariogenic their diet may be.[72] However, the view that sucrose is cariogenic is not accepted by all investigators.[73,74]

Certain plants contain *polysaccharides* which are poorly digested in the small intestine.[75] These sugars, raffinose, stachyose and verbascose, are not hydrolyzed but are fermented by Clostridium perfringens,[76] which is a part of the normal gastrointestinal flora. The fermentation can result in a great deal of flatulence which can cause much discomfort.[77]

Protein-Induced and Amino Acid-Induced Food Intolerance

Proteins and amino acids can be toxic in various illnesses. Table 3 lists many of these conditions.

Protein-Induced Food Intolerance

Celiac disease results from sensitivity to the protein, gluten, contained in wheat, rye, oats and barley.[78] The reason why gluten causes small intestinal damage is not known. Strict avoidance of gluten is necessary in the treatment of this condition. In some adult patients there may be no response to the elimination of gluten from the diet.[79,80] In dermatitis herpetiformis lesions of the gastrointestinal tract resembling those seen in gluten enteropathy may occur. The affected persons may or may not be symptomatic.[81-83] A

TABLE 3.—*Protein-Induced and Amino Acid-Induced Food Intolerance*

Protein-induced food intolerance
- Gluten intolerance
  - Celiac disease (gluten enteropathy)
  - Dermatitis herpetiformis
  - IgA deficiency and diarrhea
  - Mastocytosis
- Protein intolerance
  - Food allergy
    - Milk protein allergy
    - Soy bean protein toxicity
  - Hepatic encephalopathy in cirrhosis especially in porto-systemic shunting
  - Renal failure
  - Pancreatic insufficiency
  - Enterokinase deficiency
  - Urea cycle enzyme defects
    - Ornithine transcarbamylase deficiency
    - Argininosuccinic acid synthetase deficiency
    - Argininosuccinate lyase deficiency
    - Carbamyl phospate synthetase deficiency
    - Arginase deficiency
  - Lysine-ornithine-arginine malabsorption
  - Cystine-lysine-arginine-ornithine transport defect (cystinuria)
  - Homocystinuria
  - Succinyl-CoA:3-ketoacid CoA-transferase deficiency
  - Avidin binding of biotin

Amino acid-induced food intolerance
- Tryptophan intolerance
  - Hartnup disease
  - Tryptophan malabsorption (blue diaper syndrome)
- Phenylalanine intolerance (phenylketonuria)
- Leucine-isoleucine-valine intolerance (maple-syrup-urine disease)
- Valine intolerance (hypervalinemia)
- Leucine-isoleucine intolerance (hyperleucine isoleucinemia)
- Lysine intolerance (persistent hyperlysinemia)
- Methionine intolerance (methionine malabsorption syndrome or oasthouse urine disease)
- Leucine-induced hypoglycemia
- Monosodium glutamate intolerance (Chinese restaurant syndrome)
- Valine-isoleucine-threonine-methionine-thymine-propionate intolerance
  - Propionic acidemia
  - Methylmalonic aciduria
- Isovaleric acidemia
- β-Methylcrotonylglycine, β-hydroxyisovalericaciduria
- α-Methylacetoacetic α-methyl-β-hydroxybutyricaciduria
- Hereditary tyrosinemia
- Histidinemia
- Hyperprolinemia

gluten-free diet may be helpful in some but not all of these patients. In some patients with selective IgA deficiency and diarrhea a gluten-free diet may be effective therapy.[84] The exact relationship between IgA deficiency and the diarrhea is unknown. In one patient with mastocytosis involving the small intestine a gluten-free diet was effective in the treatment of otherwise intractable diarrhea.[85]

It is known that a variety of food proteins (such as milk, egg and wheat) can cause *allergic reactions* in susceptible people.[86-91] Often, however, definitive proof of protein allergy is lacking and such diagnoses must be considered to be presumptive. This is particularly the case when nonspecific symptoms outside of the gastrointestinal tract are attributed to a poorly defined "food allergy." The relief of symptoms by use of an elimination diet does not prove the allergic mechanism or identify the offending foods or proteins. When a particular food consistently causes gastrointestinal symptoms the possibility of an allergic reaction must be considered. However, even in these circumstances, definitive proof generally is lacking. Many foods cause urticaria, asthma and other problems, but generally the offending substance in the food has not been identified, and, again, attributing the cause to an allergic reaction is only presumptive. For example, various foods may contain substances such as tartrazine which is a common food color additive. Tartrazine may cause urticaria and asthma. It may or may not be associated with aspirin intolerance.[92] The occurrence of urticaria or asthma may be attributed to the proteins of a particular food when in fact they may be due to sensitivity to substances such as tartrazine which are added to food. The exact biochemical nature of tartrazine sensitivity is unknown. Nevertheless, there appear to be many instances in which protein allergy seems to be a reasonable possibility.[89]

In *milk allergy,* vomiting, chronic diarrhea and failure to thrive occur.[86,93-95] Malabsorption develops and eczema and eosinophilia are common. The symptoms can be reproduced with oral ingestion of milk. Allergy to cow's milk is said to be more common in atopic infants and their families than in the population at large.[96] The onset of the condition is at about one month of age. The sensitivity to milk may disappear at the age of 1 to 1½ years. Sodium cromoglycate has been used to treat milk allergy.[97]

Cases of patients with *soy bean toxicity* have been described. In a 6-week-old child, villus flattening and malabsorption developed after the ingestion of soy bean protein. Avoidance of the soy bean protein led to improvement and reingestion caused the return of the symptoms and histological abnormalities. Although an allergic reaction was considered as a possibility the authors noted that definitive proof was lacking.[98]

Patients with *food allergies* have been described although the nature of the protein to which the patient is allergic remains unknown. The case of a patient with an urticarial reaction to ingested fruit has been described.[99] In this patient vomiting also developed and sometimes diarrhea also occurred after fish was eaten. The patient's condition did not respond to therapy with sodium cromoglycate.

Eosinophilic gastroenteritis with diarrhea, peripheral eosinophilia, and eosinophilic infiltration of the small intestine has been described.[100,101] At least in one of the patients an allergic mechanism seemed to be a reasonable explanation.[100] Corticosteroid therapy is effective in this disease[100,101] but sodium cromoglycate administration is not.[101]

Protein intolerance is manifested by *hepatic encephalopathy* in cirrhosis of the liver especially if portosystemic shunting is present.[102,103] The diversion of blood away from the abnormal liver results in hyperammonemia. A low protein diet and administration of antibiotics to decrease the ammonia-producing flora of the gastrointestinal tract are necessary to control this condition.[102,103]

In *renal failure* with azotemia a normal protein intake adds to the azotemic burden.[104-106] A low protein diet is necessary if hemodialysis is not used. More recently the keto-acid analogues of essential amino acids have been used in the treatment of chronic renal failure.[107]

In *pancreatic insufficiency* there is a general deficiency of proteolytic enzymes which results in failure of protein hydrolysis and consequent protein malabsorption.[108] Replacement of pancreatic proteolytic enzymes with a suitable enzyme preparation is the proper therapy.[109-111]

In the rare condition *enterokinase deficiency* there is failure of activation of trypsinogen and chymotrypsinogen.[112-114] Consequently, there is failure of digestion of protein in the small intestine and protein malabsorption results. Enterokinase is an enzyme of the small intestine. There are data to suggest that the activation of trypsinogen to trypsin and chymotrypsinogen to chymotrypsin occurs at the surface of the small intestinal epi-

thelial cell.[115] However, the exact localization of enterokinase is not certain. Recent studies suggest that enterokinase activity in the intestines of rats is mainly in a free form in intestinal mucin and is present only to a negligible extent in the brush border.[116] The condition can be difficult to diagnose.[113] Treatment is effected with pancreatic extract.

There is a large number of *disorders of amino acid metabolism*. Many of these diseases involve defects in amino acid transport[117] and enzyme deficiencies. In many instances these defects render the affected person susceptible to dietary protein or specific amino acids, or both. Restriction of dietary protein or specific amino acids may correct some or all of the biochemical abnormalities and clinical manifestations of the disease. Additional measures may be helpful or the treatment of choice. Since dietary protein or amino acids in the usually recommended amounts aggravate the condition these disorders represent protein and amino acid intolerances. Not all disorders of amino acid metabolism are aggravated by normal protein or amino acid intakes or helped by dietary restriction. These amino acid disorders will not be covered here. Many amino acid disorders are exceedingly rare with only one or two patients described and with no information available about the effect of diet on the clinical or biochemical manifestations of the disorder. These disorders also will not be discussed.

Defects of *urea cycle enzymes* (ornithine transcarbamylase, argininosuccinic acid synthetase, argininosuccinate lyase, carbamyl phosphate synthetase, arginase) result in hyperammonemia with normal protein intakes.[118] The hyperammonemia results from the decreased ability of the liver to handle the ammonia derived from the dietary amino acids. Hyperammonemia is manifested by irritability, ataxia, lethargy, coma and mental retardation. Different defects of the urea cycle enzymes have varying degrees of severity. A low protein diet may be successful, but not always, in treating this group of diseases.

A defect involving the kidney and small intestine in the absorption of basic amino acids (lysine, ornithine, arginine) has been termed *hyperdibasic-aminoaciduria*.[119-121] In this condition lysine competed with arginine transport. The disease is manifested by diarrhea, periodic hyperammonemia, vomiting and malaise. A low protein diet controls the manifestations of the disease but may lead to growth failure and central nervous system abnormalities. Supplementation with citrulline plus lysine has been reported to be beneficial together with a low protein diet.[121]

In *cystinuria* there is an increased urinary excretion of cystine, lysine, arginine and ornithine with the formation of cystine renal tract calculi. The defect is related to defective transport of these amino acids in the small intestine and kidney.[122] Treatment consists of maintaining a high urine volume[122] and therapy with pencillamine[124] which forms a mixed disulfide with cystine. A low protein[125] or low methionine diet[126] may decrease urinary cystine but not all investigators have been able to show this result.[127]

Homocystinuria[128,129] is characterized by elevated plasma concentrations of methionine and homocystine and increased urinary homocystine excretion. Less constant features are mental retardation, fair complexion and growth failure.[129,130] Dislocation of the lens is common. Arterial and venous thromboses are a major cause of death.[130] Homocystinuria is the result of at least three separate enzyme deficiencies.[130] Cystathionine synthase deficiency is the most common cause of homocystinuria. A deficiency in the formation of deoxyadenosylcobalamin and methylcobalamin leads to a combination of homocystinuria and methylmalonic aciduria. Homocystinuria can also occur when there is a deficiency of methylene tetrahydrofolate reductase. A low-protein low-methionine diet can reduce the elevated plasma methionine and decrease the plasma homocystine especially when supplemented with cystine[131] although cystine may not be required in those patients with residual enzyme activity. Although this dietary approach is encouraging in preventing mental retardation and ectopia lentis in infants it does not repair the dislocated lens and the mental retardation in older children. Pharmacological doses of vitamin B_6 (250 to 500 mg per day)[132] eliminate the chemical abnormalities in many but not all patients with cystathionine synthase deficiency.[130] In the vitamin B_6-responsive form of disease this is the treatment of choice. Treatment of the other types of homocystinuria is discussed in the section on methylmalonic aciduria.

One patient with *succinyl-CoA:3-ketoacid CoA-transferase deficiency* has been reported. This enzyme deficiency was discovered in an infant who had severe, intermittent ketoacidosis. The episodes of severe ketoacidosis were precipitated by either an acute infection or by the ad-

ministration of protein. With glucose alone the infant did well and had minimal ketonuria. The patient died of pneumonia at 6½ months of age.[133]

Raw egg white contains a protein termed avidin which binds biotin tightly. Chronic ingestion of raw egg white can produce biotin deficiency.[134] Avidin is denatured when egg white is cooked and loses its ability to bind biotin.

Amino Acid-Induced Food Intolerance

Hartnup disease results from tryptophan malabsorption which in turn leads to cerebellar ataxia, an intermittent photosensitive pellagra-like rash and mental retardation.[135] It has been suggested that the decreased absorption of tryptophan leads to increased indole formation which inhibits nicotinamide synthesis from tryptophan. The nicotinamide deficiency further depresses tryptophan absorption.[136] Treatment with nicotinamide ranging in dosage from 40 to 250 mg per day has resulted in pronounced clinical improvement.[137]

In *tryptophan malabsorption* (the blue diaper syndrome) there is abnormal small intestinal absorption of dietary tryptophan.[138] There is increased production of indican and indoles which appear in the urine. One of the indoles, indigo blue, is responsible for the blue color of the diapers.

Phenylketonuria is caused by a deficiency of hydroxylation of phenylalanine to form tyrosine.[139] Various metabolities of phenylalanine accumulate and mental retardation[140] results although the exact mechanism is unknown. Treatment consists of providing a low phenylalanine diet in order to prevent hyperphenylalaninemia and the accumulation of the presumably toxic metabolites.[140] Care must be taken not to give a diet too low in phenylalanine since phenylalanine deficiency may impair protein synthesis.

A milder form of phenylketonuria has been described in which a higher phenylalanine intake can be tolerated. In classical phenylketonuria, plasma phenylalanine levels can be kept below 1 mM by providing 250 to 500 mg per day of phenylalanine. As noted, in the milder form a higher phenylalanine intake can be tolerated.[141] The reason for this increased tolerance for phenylalanine is unknown.

Another variant form exists secondary to a deficiency of dihydropteridine reductase which generates the pteridine cofactor (tetrahydrobiopterin) necessary for phenylalanine hydroxylase function.[142,143] In one patient, despite prompt treatment with a low phenylalanine diet and excellent control of serum phenylalanine, progressive intractable seizures occurred. Enzyme deficiency was shown in the brain, liver and skin fibroblasts.

Classical phenylketonuria and its variants must be distinguished from transient phenylketonuria,[144] hyperphenylalaninemia without phenylketonuria[145] and transient neonatal hyperphenylalaninemia.[146]

Maple-syrup-urine disease (MSUD) results from a defect in the metabolism of the keto-acid analogues of the branched-chain amino acids (leucine, isoleucine, valine) due to an abnormality of the multienzyme complex (failure of oxidative decarboxylation) which is involved in the metabolism of these keto-acid analogues.[147] The presence of these compounds in the urine gives rise to the odor of maple syrup. In the severe or classical form there are feeding difficulties, vomiting, hypertonicity and a shrill cry in the first week of life. Flaccidity and apnea may occur. Deep tendon reflexes may disappear. Convulsions occur and death may happen early in life. Untreated children have physical and mental retardation.[148,149] Therapy requires severe dietary restriction of branched-chain amino acids from early postnatal life.[150]

The intermittent form of MSUD occurs in late infancy or childhood. Intermittent episodes of illness occur which may be severe. There are lethargy, vomiting and neurological manifestations. The urine has the characteristic odor of maple syrup. The acute episode may be precipitated during a concurrent illness or during an abrupt increase in protein intake.[151] Branched-chain keto-acid oxidation is deficient but not as severe as in the classical form but the exact nature of the defect is not clear.[152] During acute attacks peritoneal dialysis and a restricted branched-chain amino acid diet is recommended. A low protein diet during asymptomatic periods should be maintained as a preventive measure.[151]

A mild form of MSUD has been described[153] in an infant with defective branched-chain keto-acid oxidation with elevated plasma and urine levels of valine, leucine, isoleucine, alloisoleucine and their keto-acid analogues. Dietary administration of branched-chain amino acids caused a further increase in the plasma and urine levels and mild symptoms of irritability and vomiting occurred.

Dietary restriction of branched-chain amino acids corrected the chemical abnormalities.

Another milder variant of MSUD has been treated successfully with thiamine.[154] The multienzyme complex utilizes thiamine as one of its cofactors.[147] In the thiamine-responsive form of disease it may be that the defect is related to decreased thiamine-binding.

Hypervalinemia[155] occurs because of a deficiency of valine transaminase[156] and is manifested by vomiting, lethargy, failure to thrive, mental and physical retardation, nystagmus, and increased urine and plasma levels of valine. Clinical symptoms and hypervalinemia can be corrected by a low valine diet.[157]

Hyperleucine-isoleucinemia[158] is due to a partial defect in leucine and isoleucine transamination. The clinical manifestations are failure to thrive, mental retardation, convulsions, retinal degeneration, apparent nerve deafness, and increased plasma levels of leucine and isoleucine. Leucine loading increases plasma leucine levels higher and longer than normal. Restriction of dietary protein or leucine and isoleucine reduces plasma amino acid levels to normal.

Lysine intolerance is due to a deficiency of the enzyme lysine dehydrogenase which is involved in the lysine metabolic pathway.[159] This deficiency is believed to result in lysine accumulation with consequent inhibition of the enzyme arginase, resulting in impairment of the urea cycle.[160] This results in hyperammonemia with nausea, vomiting and lethargy. Therapy consists of a low protein or low lysine diet.[161] It has been suggested that wheat can be used in the diet because of its relatively low lysine content.[161]

Persistent hyperlysinemia is characterized by elevated plasma and urinary concentrations of lysine,[162] mental retardation, muscular hypotonia and lax ligaments. After oral lysine loads, plasma lysine rises higher and longer than in control subjects. In some patients there are no abnormal clinical manifestations.[163] In some patients there appears to be a deficiency of lysine:α-ketoglutarate reductase.[164]

The *methionine malabsorption syndrome,* or oasthouse urine disease, has been described in two patients with white hair, edema, hyperpneic attacks, convulsions, mental retardation and urine that had the odor of dried celery.[165] One infant died. The second infant had diarrhea with the ingestion of methionine and the stools contained large amounts of methionine.[166] It was concluded that this condition resulted from a defect in methionine absorption. The second patient was treated with a methionine-restricted diet which controlled the diarrhea and caused disappearance of the convulsions and urinary odor.[167] The mental retardation persisted, however.

In certain susceptible children *leucine has been found to cause hypoglycemia.*[168] This group of children was separated from a larger group of children who had previously been diagnosed as having idiopathic hypoglycemia of childhood.[169] In this group of children leucine appears to cause an increased release of insulin.[170] Although a low leucine diet is effective,[171] sodium glutamate or diazoxide (or both) is a more convenient agent for treatment.[172,173] In patients with islet cell neoplasms, hypoglycemia may develop following leucine ingestion.[174] Infrequently adult patients have hypoglycemia related to leucine sensitivity.[172] Hypoglycemia in such patients is aggravated by a high protein, low carbohydrate diet.[172] Leucine can potentiate the action of sulfonylurea compounds and lower blood glucose levels in normal subjects.[175]

After eating Chinese food some persons note the onset of a syndrome characterized by a burning sensation, facial pressure, headache and chest pain.[176] This so-called *Chinese restaurant syndrome* has been attributed to the monosodium glutamate added to the food.[176,177]

Leucine, valine, isoleucine, threonine and methionine are metabolized ultimately by way of a common pathway, the propionic acid pathway.[178,179] The contribution of leucine is relatively small. Thymine also is catabolized to form propionic acid. Defects of enyzmes in this pathway may give rise to a variety of rare conditions. *Propionic acidemia* occurs when there is a deficiency of propionyl-CoA carboxylase, a biotin-dependent enzyme. This results in the accumulation of propionic acid and its metabolites, butanone, pentanone and hexanone.[180,181] The condition is manifested by recurrent attacks of ketoacidosis and neutropenia aggravated by infections and a high protein diet. The condition has variable severity ranging from death to relatively mild symptoms with mental retardation.[182] Treatment has been accomplished using a low protein diet.[183] In one patient with propionic acidemia, pharmacological doses of biotin were found to be effective.[184]

Defects in the enzymes methylmalonyl-CoA mutase, a vitamin B_{12}-dependent enzyme and methylmalonyl-CoA racemase cause *methylma-*

lonic aciduria (MMA). The condition is manifested by severe ketoacidosis soon after birth or in early infancy, failure of growth and development, protein intolerance, neutropenia and in many cases death.[185,186] In the enzyme deficient forms of MMA there are defects in the apoenzymes and therefore the apoenzyme deficient types are not vitamin B_{12} responsive.[185,186] Treatment of these diseases consists of restricting dietary protein or a combination of dietary valine, thymine and propionate. There are two vitamin B_{12}-responsive forms in which there is a defect in the synthesis of the vitamin B_{12} coenzyme deoxyadenosylcobalamin or both deoxyadenosylcobalamin and methylcobalamin.[185,186] Treatment of these two forms of MMA is accomplished with pharmacological doses of vitamin B_{12} in many cases.

Isovaleric acidemia occurs in early infancy. In this disease there are severe metabolic acidosis, ketosis, lethargy and neurological symptoms, and death may occur. Mental retardation may result in untreated patients.[187,188] The urine usually has a pungent sweat-like odor caused by isovaleric acid. Isovaleric acid is increased in concentration in the serum and urine. There is a defect in isovaleryl-CoA dehydrogenase. The condition is treated with a restricted leucine intake[188] or a low protein diet.[188]

β-Methylcrotonylglycine, β-hydroxyisovalericaciduria is caused by a deficiency of a biotin-dependent carboxylase in the leucine catabolic pathway. One patient with this disease had urine that had the odor of cat's urine due to the presence of β-methylcrotonylglycine and β-hydroxyisovaleric acid.[189] The patient had muscular hypotonia and atrophy and retarded motor development. The restriction of dietary leucine decreased the β-hydroxyisovaleric acid but did not alter the excretion of β-methylcrotonylglycine.[190] In a second patient[191] vomiting, irritability, a skin rash and acidosis occurred. Only β-hydroxyisovaleric acid was increased in the urine. The patient's condition responded to pharmacological doses of biotin (10 mg per day).

In *α-methylacetoacetic α-methyl-β-hydroxybutyricaciduria* there is late onset intermittent metabolic acidosis. The urine has increased amounts of α-methyl-β-hydroxybutyric acid, α-methylacetoacetic acid and n-butanone. These metabolites increase further with increased dietary protein or isoleucine. The acidosis is controlled by a low protein, high calorie diet.[192,193] The disorder is caused by a defect in the catabolism of isoleucine.

Hereditary tyrosinemia is caused by a deficiency of p-hydroxyphenylpyruvic acid oxidase which transforms p-hydroxyphenylpyruvic acid into homogentisic acid[194] in the tyrosine metabolic pathway. The acute form of the disease occurs in the first six months of life. Most of the patients die of liver failure.[195] The urine has a cabbage-like odor[196] probably due to a methionine derivative. The islets of Langerhans are hyperplastic and associated hypoglycemia occurs. In the chronic form nodular hepatic cirrhosis, islet cell hyperplasia, hypoglycemia, nephropathy and failure to thrive occur.[197] The nephropathy causes a Fanconi syndrome and hyperphosphatemic rickets. The urine contains large amounts of tyrosine, p-hydroxyphenylpyruvic acid and p-hydroxyphenyllactic acid,[198] and blood tyrosine and methionine concentrations are elevated. There is increased formation and excretion of δ-aminolevulinic acid and symptoms similar to those of acute porphyria are seen. Catecholamines are increased and may cause hypertension.[199] Restriction of dietary tyrosine, phenylalanine and methionine is beneficial in treating this disease.[200,201] Care must be taken not to restrict dietary amino acids too severely since amio acid deficiency may develop.[202]

In *histidinemia* there may be mental retardation and speech abnormalities but their relationship to the histidinemia is unclear.[203] Blood histidine is elevated while serotonin levels are decreased.[204] In this disease there is deficiency of L-histidine ammonia-lyase (histidase).[205] Although there have been treatment failures with a restricted histidine diet,[206] successful control can often be accomplished.[204,207,208] However, recent studies suggest that histidinemia may be benign and that dietary therapy may not be necessary.[208]

In *type I hyperprolinemia* there is a deficiency of proline oxidase which converts proline to Δ′-pyrroline-5-carboxylic acid (PC) which results in elevated blood proline levels and which may be associated, but not always, with mental retardation, renal disease and seizures.[209,210] The exact relationship between the enzyme defect and the clinical manifestations is not clear. *Type II hyperprolinemia* is due to a defect in PC dehydrogenase[211] and causes elevated blood proline and may be associated with mental retardation and seizures although the exact relationship is unclear.[211] Plasma proline levels can be decreased to normal in both of these conditions using a restricted proline intake.[209] In one patient the

associated seizures and intestinal dysfunction were also controlled with a restricted proline diet.[210]

Lipid-Induced Food Intolerance

In Table 4 various conditions are listed in which lipid intolerance occurs.

Steatorrhea occurs whenever lipid malabsorption occurs.[212,213] Steatorrhea represents an intolerance to dietary lipid. Lipid malabsorption occurs in pancreatic insufficiency,[108] various types of small intestinal diseases,[212,213] hepatobiliary disease,[212,213] the short-bowel syndrome,[214] lymphatic obstruction and intestinal lymphangiectasia,[215] mesenteric artery insufficiency,[216,217] and pancreatic endocrine diseases such as diabetes mellitus[218] and the Zollinger-Ellison syndrome.[219] Various nonpancreatic endocrine diseases also may cause malabsorption.[212] Although lipid has been thought to provoke symptoms in gall bladder disease several studies have been unable to corroborate this belief.[220,221]

In *type I hyperlipoproteinemia* there is severe fasting hyperchylomicronemia, pronounced elevations of plasma triglyceride, eruptive xanthomas on the skin and recurrent episodes of abdominal pain due to pancreatitis.[222] The condition is caused by an absence of lipoprotein lipase.[223] A low fat diet can control the disease process.[222] A patient with a deficiency of apolipoprotein C-II has been described in whom lipoprotein lipase activity was deficient.[224] Apolipoprotein C-II is a component of chylomicrons and is an essential activator of lipoprotein lipase.[225] Replacement of apolipoprotein C-II was effective in activating lipoprotein lipase.[224] In *type V hyperlipoproteinemia* there are hyperchylomicronemia and elevated plasma triglyceride levels.[222] Dietary treatment involves a low fat diet and weight reduction by means of a reduced caloric intake.[222]

Carnitine palmitoyltransferase deficiency is a rare disorder of muscle which causes rhabdomyolysis and recurrent myoglobinuria. The enzyme deficiency results in an impairment of fat oxidation. Hypertriglyceridemia is present in this disorder.[226,227] Complete[226] and partial deficiency[228] of the enzyme has been reported. Exercise, fasting especially with exercise, and a low carbohydrate diet can provoke attacks of rhabdomyolysis. The condition can be managed by providing a low fat diet similar to that used for patients with type I hyperlipoproteinemia.[228]

Tangier disease is characterized by the absence of plasma high-density lipoprotein and the accumulation of cholesteryl esters in the cornea, peripheral nerves, and the reticuloendothelial cells of the tonsils, spleen, bone marrow, lymph nodes, thymus, intestinal mucosa and skin.[229,230] Abnormal high density lipoproteins are found in the plasma and appear to be abnormal products of chylomicron metabolism[231] which are phagocytosed by macrophages of the reticuloendothelial system.[231] Restriction of dietary fat reduces the level of the abnormal lipoproteins.[231]

In persons who are unable to metabolize the branched chain lipid phytanic acid, a chronic

TABLE 4.—*Lipid-Induced Food Intolerance*

Malabsorption syndromes
- Pancreatic insufficiency
  - Cystic fibrosis
  - Pancreatitis
  - Carcinoma
  - Other causes
- Small intestinal disease
  - Tropical sprue
  - Celiac disease
  - Regional enteritis
  - Scleroderma
  - Lymphoma
  - Collagenous sprue
  - Mastocytosis
  - Multiple small intestinal diverticula
  - Amyloidosis
  - Immunoglobulin deficiency with lymphoid nodular hyperplasia
  - Macroglobulinemia with infiltration of the bowel wall
  - Short bowel syndrome
  - Other causes
- Hepatobiliary disease
- Lymphatic disease
  - Whipple disease
  - Lymphangiectasia
  - Lymphatic obstruction
  - Other causes
- Vascular disease
- Pancreatic endocrine disease
  - Diabetes mellitus
  - Zollinger-Ellison syndrome
- Nonpancreatic endocrine disease
  - Carcinoid
  - Thyrotoxicosis
  - Medullary carcinoma of the thyroid
  - Hypoparathyroidism

Hyperchylomicronemia
- Type I hyperlipoproteinemia
  - Lipoprotein lipase deficiency
  - Apolipoprotein C-II deficiency
- Type V hyperlipoproteinemia

Hypertriglyceridemia due to carnitine palmitoyltransferase deficiency

Tangier disease

Refsum disease due to phytanic acid α-hydroxylase deficiency

Sitosterol intolerance

slowly progressive neurological syndrome called *Refsum disease* (heredopathia atactica polyneuritiformis) occurs.[232] A diet deficient in phytanic acid, which is present in dairy and ruminant fats and which is derived from the phytol of chlorophyll, decreases the serum phytanic acid level and appears to lead to symptomatic improvement.[233]

Two sisters have been described who had elevated plasma levels of the plant steroid sitosterol, and accumulation of sitosterol in red blood cells, tendon xanthomata, adipose tissue and skin surface lipids.[234] There were lesser amounts of campesterol and stigmasterol also present. Serum cholesterol levels were normal. There was increased absorption of sitosterol by the small intestine. A sitosterol-free diet decreased the sitosterol accumulation in the patients' plasma and tissues. This rare entity has been termed *β-sitosterolemia and xanthomatosis*. The case of another patient with the same disorder and hypercholesterolemia has been reported.[235]

The relationship between dietary cholesterol and other lipids, serum cholesterol and lipoproteins, and the development of atherosclerotic coronary artery disease is a complex problem and is treated elsewhere in this symposium.

Mineral-Induced Food Intolerance

In Table 5 are listed those food intolerances related to minerals.

Sodium taken in excess may lead to hypertension. The exact relationship between sodium intake and the development of hypertension is still in dispute. It may be that sodium is an aggravating feature for those persons genetically disposed to hypertensive vascular disease. It is not possible here to review the subject in any but the most cursory fashion. However, there is some experimental and clinical evidence that implicates sodium as an important factor in the pathogenesis of hypertension.

It is known that in animals given a high sodium intake, hypertension can develop.[236] Obese patients with hypertension can be made normotensive on an isocaloric low sodium diet while a high sodium low calorie diet will result in weight loss but no change in the hypertension.[237] However, a more recent study showed a decrease in hypertension with reduction in weight without any ostensible change in dietary sodium.[238] A sodium-sensitive strain of rats has been bred.[239-242] In this sensitive strain of animals, hypertension developed with a high sodium diet and there was decreased survival. Another strain resistant to sodium was also developed. This group of animals remained normotensive on a high sodium diet and lived a normal life span. The Japanese in northern Japan have an extremely high salt intake.[243] Hypertension and strokes are common in this group. Hypertension is closely associated with sodium retaining conditions such as the Cushing syndrome,[241] primary hyperaldosteronism and other syndromes involving hypersecretion of various adrenocortical steroids,[245,246] and chronic licorice ingestion.[247] Hypertension due to primary aldosteronism or primary mineralocorticoid excess appears to be due to volume expansion secondary to sodium retention. In hypertensive states associated with secondary aldosteronism the extra-adrenal stimulus causing the elevation in aldosterone leads to activation of the renin-angiotensin system.[246] A low sodium diet[248,249] or diuretic

TABLE 5.—*Mineral-Induced Food Intolerance*

Sodium intolerance
Hypertension
Edema
Congestive heart failure
Cirrhosis and ascites
Renal failure
Cyclic edema
Other causes
Precipitation of paralysis in familial hypokalemic periodic paralysis
Potassium intolerance
Precipitation of paralysis in familial hyperkalemic periodic paralysis
Renal failure
Addison disease
Potassium-sparing diuretic agents
Selective hypoaldosteronism
Other causes
Iron intolerance
Hemochromatosis
Dietary-induced hemosiderosis
Copper intolerance
Hepatolenticular degeneration (Wilson disease)
Iodine intolerance
Hyperthyroidism (jodbasedow)
Hypothyroidism
Calcium intolerance
Pseudoxanthoma elasticum
Phosphate intolerance
Renal failure
Tetany in infants
Fluoride intolerance
Fluorosis

therapy[249] are often successful in controlling mild to moderate hypertension. In patients with essential hypertension, sodium balance determines the degree of participation of the renin-angiotensin system in sustaining high blood pressure.[250] Even the low-renin type of hypertensive patient can become renin dependent with sufficient sodium depletion. Recently it has been shown that spontaneously hypertensive rats probably have a leak of calcium from their vascular smooth muscle membranes that is only partially compensated by the calcium transport mechanism,[251] as well as leakage of sodium, potassium and chloride.[252] Whether these defects in the rat are in any way related to possible defects in the vascular smooth muscle of humans remains to be seen.

There are, therefore, several pieces of evidence which implicate sodium as being at least one of the factors involved in the pathogenesis of hypertension, although different mechanisms may be operative in different hypertensive diseases.

Sodium aggravates edema from many causes such as congestive heart failure,[253] cirrhosis with ascites,[254] renal failure,[255] and cyclic or metabolic edema.[256] In some obese patients who fast to lose weight, significant edema develops when they resume eating.[257] This has been related to the suppression of hyperglucagonemia that occurs during fasting.[258] Glucagon has a natriuretic effect which disappears when a normal food intake results in suppression of the elevated glucagon levels. A high sodium diet may provoke paralysis in persons with familial hypokalemic periodic paralysis,[259] but this is not invariably true.[260]

Potassium can be toxic in certain special situations. Potassium may precipitate paralysis in cases of familial hyperkalemic periodic paralysis (Gamstorp disease or adynamia episodica hereditaria).[261] In renal failure potassium ingestion may aggravate preexisting hyperkalemia which can cause death.[255] Potassium may also cause hyperkalemia in such conditions as Addison disease,[262] diuretic therapy together with a potassium sparing agent (such as triamterene),[264] selective hypoaldosteronism[264-266] and so on.

In hemochromatosis *iron* gradually accumulates and leads to cirrhosis, diabetes, cardiac and pituitary disease, skin pigmentation and hypogonadism.[267-269] In this condition treatment with a low iron diet is not practical. The most efficacious therapy for hemochromatosis is phlebotomy.[267] Increased intake of iron can lead to so-called dietary-induced siderosis.[267,270]

In hepatolenticular degeneration or Wilson disease the accumulation of copper leads to a slowly progressive cirrhosis or cerebral degeneration (or both) and a resulting fatal neurological disease.[271-275] Treatment with a low copper diet is not practical. Treatment with penicillamine, which chelates copper and leads to a decrease in body copper stores, is quite successful and may prevent progression or development of the disease.[272]

Iodine intake may precipitate the development of hyperthyroidism, the so-called jodbasedow.[276] The mechanism whereby iodine precipitates hyperthyroidism is not certain. Persons who live in a region where iodine is deficient may have a highly effective iodine trapping mechanism within the thyroid which allows them to sequester the small amounts of iodine in their food.[276,277] When such persons move to another region where the levels of iodine are much higher or ingest iodide medication[278] or iodine-supplemented foods, hyperthyroidism may be precipitated.[276,279] The dosage of iodide[276] and the presence of thyroid disease[278] seem to be important factors in the pathogenesis of the disease. In other persons the chronic ingestion of large amounts of iodine may result in hypothyroidism.[280,281] Maternal ingestion of iodide can cause congenital goiter and hypothyroidism.[280] Often the iodides have been used as medication.[281] Myxedema has been caused by small, pharmacologic doses of iodide in patients with diffuse toxic goiter rendered euthyroid by radioiodine or surgical treatment.[281]

Calcium may be toxic in pseudoxanthoma elasticum. In this disease there is calcification of elastic fibers of the skin, retina and blood vessels leading to extensive skin lesions, progressive loss of vision and arterial disease.[282] It has been found that on a high calcium diet there is progression of the calcification which ceases when a low calcium diet is substituted.[283] Lesions can be prevented from developing in affected patients with the use of a low calcium diet. In pseudoxanthoma elasticum the abnormal elastic fibers have been shown to have an increased affinity for calcium *in vitro*.[284]

A high *phosphate* diet in renal failure may aggravate already existing hyperphosphatemia and hypocalcemia. As a result of the hypocalcemia, neuromuscular irritability and parathyroid hyperplasia occur.[285] Chronic persistent hyperphosphatemia and hypocalcemia results in stimulation

of parathyroid hormone secretion and consequent resorption of bone. In chronic renal failure there is sustained elevation of serum phosphate because of the inability of the kidney to excrete phosphate.

Control of phosphate absorption with phosphate-binding gels and use of vitamin D and calcium will decrease serum phosphate and increase serum levels of calcium.[286] Oral[287] and intravenous[288] administration of phosphate can cause a decrease in plasma calcium in hypercalcemic and normocalcemic persons. In experimental animals renal calcification can be prevented by phosphate restriction.[289] Extraskeletal calcification has been produced with orally given phosphate.[290-292] Oral administration of phosphate supplement in man and in dogs increases circulating immunoreactive parathyroid hormone.[293,294] Infants without renal failure may have tetany when fed cow's milk[295,296] which has a calcium to phosphate ratio of 1:1, compared with human milk which has a 2:1 ratio. The amount of phosphate fed exceeds the amount filtered by the kidney at normal serum levels. As a result of hyperphosphatemia, hypocalcemia and tetany occur. During pregnancy tetany and leg cramps are prone to occur in some women. Both have been attributed to the increased phosphate intake in milk together with the increased drain on calcium by the fetus.[297,298] The specific cause of the leg cramps (which occur usually between the 24th and 34th weeks of pregnancy), however, has not been established.

Fluoride is an essential trace mineral for many animals and is thought to be essential for man, although definitive proof is lacking.[299] It is well known that an excess intake of fluoride (usually in water) that naturally occurs in certain areas of the world (such as India) can cause a bone disease, fluorosis, which is characterized by osteosclerosis, periosteal new bone deposition, osteophyte formation, and ossification of tendons and ligaments. Severely fluorotic bone is friable. In this condition serum parathormone is elevated. Symptoms and signs include skeletal pain, backache, stiffness, limitation of motion of joints and flexion deformities. With a smaller intake of fluoride only mottling of the teeth may occur. A low calcium diet may cause improvement.[300] The amount of fluoride added to the water supply to prevent dental caries is well below the level of fluoride necessary to cause fluorosis or mottling of the teeth.

Other minerals are known to be essential for man. These include magnesium, cobalt, chromium, manganese, molybdenum, selenium and zinc. Elsewhere in this symposium the clinical importance of zinc is considered. Toxicity of these minerals usually occurs through industrial exposure and not by ingestion of the usual diet. Cardiomyopathy has been related to beer containing cobalt but other factors were implicated as well.[302] Selenium is quite toxic but toxicity does not result from ingestion of the usual diet. Selenium is an essential trace mineral serving as a cofactor of the enzyme glutathione peroxidase.[303]

TABLE 6.—*Vitamin-Induced Food Intolerance*

Vitamin A toxicity
Vitamin D toxicity
Nicotinic acid intolerance
Flushing of skin
Abnormal findings on liver function studies
Atypical cystoid macular edema
Carotene intolerance
Hypercarotenemia due to 15,15'-dioxygenase deficiency
Hypercarotenemia in hypothyroidism

Vitamin-Induced Food Intolerance

Table 6 lists those vitamins that can cause toxicity when ingested in excess amounts.

Hypervitaminosis A results from excess ingestion of vitamin A.[304,305] This is characterized by hair loss, desquamation, pigmentation, hepatomegaly, fatigue, insomnia, and bone or joint pain. Excess ingestion of vitamin D in infants and children results in hypercalcemia, anorexia, nausea, vomiting, weight loss and azotemia.[306,307] In adults, polyuria, dehydration, hypokalemic alkalosis, mental confusion, azotemia, bone resorption and metastatic calcification may occur as well.[308]

Nicotinic acid has been used in pharmacological amounts (1.5 to 9 grams per day) to treat patients with hyperlipoproteinemia (types II, IV, and V).[309] In some patients vasodilation of skin capillaries will develop with flushing and an increased skin temperature which can be uncomfortable, therefore limiting the use of nicotinic acid.[310-312] In some patients abnormal findings on liver function tests may occur although no histological abnormality occurs. Rarely jaundice will occur. Large doses of nicotinic acid also have been reported to cause pruritus, abdominal discomfort, hyperuricemia, hyperglycemia and postural hypotension. These effects are probably chemical effects and unrelated to the vitamin function of nicotinic acid. Atypical cystoid macular

TABLE 7.—*Multiple Food Intolerances*

Anorexia nervosa
Malabsorption syndromes
Food allergies
Splanchnic vascular insufficiency
Anorexia in systemic illnesses
Primary disorders of smell and taste
Nutritional recovery syndrome
Adult formiminotransferase deficiency
Gustatory sweating
Psychological disturbances

edema with loss of central vision has been reported also in patients using pharmacological amounts of nicotinic acid.[313] Vision improved and macular edema resolved with discontinuation of the nicotinic acid administration.

Hypercarotenemia has been described in a few patients who had a deficiency of the enzyme 15,15′-dioxygenase which cleaves β-carotene into vitamin A.[314] Absence of this enzyme results in the absorption of carotene and the subsequent discoloration of the skin. Hypercarotenemia should not be mistaken for jaundice since the sclerae are not affected in hypercarotenemia. The 15,15′-dioxygenase is regulated by thyroid hormone. In hypothyroidism, therefore, hypercarotenemia will develop depending on the level of β-carotene in the diet.[315]

Multiple Food Intolerances

Multiple food intolerances are common medical problems. In Table 7 certain examples of multiple food intolerances are tabulated. In *anorexia nervosa* the person rejects food in general and is unable to maintain normal body weight. Various psychiatric interpretations have been given to explain the pathogenesis of anorexia nervosa.[316-320] As yet, however, the cause is not known.

In the various *malabsorption syndromes* listed in Table 4 many different foods may contribute to diarrhea and steatorrhea. In a rare condition, *adult formiminotransferase deficiency,* there are multiple food intolerances.[321] In this condition the enzyme formiminotransferase is deficient in the jejunum, liver and red blood cells, at least. Formiminotransferase transforms tetrahydrofolate into the formimino derivative. Formiminoglutamic aciduria is present even without histidine loading. We have carried out studies in a patient with this condition in whom there was failure of jejunal glycolytic enzymes to adapt to dietary carbohydrates. Dietary carbohydrates induced anorexia, nausea, vomiting, diarrhea, lightheadedness and syncope. In addition, various proteins caused diarrhea. The exact relationship between the formiminotransferase deficiency and the food intolerance is unclear.

As already discussed, various foods are thought to cause illness because of *allergy.* A person may be sensitive to a number of foods. Although an allergic mechanism may be invoked it is not always clear that the food intolerances are indeed caused by an allergy.

Splanchnic vascular insufficiency can cause abdominal pain after eating.[322] This is a nonspecific food intolerance and is not related to any particular food substance. The abdominal pain in this condition is the result of gastrointestinal ischemia.

Another type of multiple food intolerance is that which occurs with various systemic diseases of an acute or chronic nature in which *anorexia is a nonspecific symptom.* Anorexia occurs in a great number of illnesses, especially acute and chronic infections and inflammatory conditions and in neoplastic diseases.[323,324] The mechanism of anorexia in these conditions is not well understood. It has been postulated that in neoplasia the tumor cells produce anorexigenic peptides.[325] Primary disorders of smell and taste may cause an aversion to food. *Dysgeusia or anosmia* may lead to food rejection.[326] Treatment with zinc sulfate has been advocated for this disorder;[326] however, not all of the affected patients can be treated successfully with zinc sulfate.[327,328] This problem is discussed more fully elsewhere in this symposium.

Psychological disturbances may lead to food rejection or food faddism.[329] Food preferences, however, are conditioned by socioeconomic-cultural-religious factors.[330-331] Neuroses and psychoses may be associated with abnormalities of food intake.[332] Psychological disturbances often have been invoked to explain the compulsive eating that leads to obesity.[333,334] The problem of obesity is discussed elsewhere in this symposium.

Persons who are fasting or starving will become ill if they quickly resume a normal dietary intake.[335] This condition has been termed the *nutritional recovery* syndrome and is characterized by abdominal distention, ascites, hepatomegaly, splenomegaly, hypertrichosis, parotid swelling, gynecomastia and eosinophilia. Nausea and vomiting may also occur.

Facial sweating may occur in certain people

TABLE 8.—*Therapy for Food Intolerance*

Identify the offending food or food component
Treat the basic disease if food intolerance is a secondary consequence
Avoid the offending food or food component
Increase the activity of any deficient enzyme, if possible

after eating different foods.[336] This is particularly true in patients with diabetic autonomic neuropathy. Ingestion of cheese particularly may result in *gustatory sweating*. Atropine and oral cholinergic drugs may be successful in controlling this condition.[337]

Idiopathic Food Intolerance

Finally, we must consider those foods which cause illness for unknown reasons. It is not possible to consider every food that has been reported to cause symptoms or illness. It is difficult to determine what component or components of a given food cause the difficulty. Some of the foods that are reported to cause illness include liver, chicken, beets,[338,339] cucumbers, Worcestershire sauce[340,341] and curry.[342] A large number of people dislike liver and many report that liver causes nausea and vomiting or diarrhea. Some patients are intolerant of chicken. In a rare patient beets have caused shock with the appearance of beet pigment (betanin) in the urine.[338,339] Similarly, cucumbers have been reported to cause shock. There is a question as to whether the heavy use of Worcestershire sauce may cause renal disease.[340,341] There are suggestions that the use of curry may cause renal damage.[342] Anaphylactic shock is well described in certain persons who are sensitive to nuts and shellfish.[89] In many instances the reports of food intolerance are anecdotal and poorly documented.

Therapy for Food Intolerance

When faced with the problem of food intolerance the systematic approach outlined in Table 8 is a convenient plan to follow. The offending agent in the food or the particular nutrient itself should be identified, if possible. If the food intolerance is secondary to a particular disease this should be treated. In primary food intolerance the offending agent or food can be avoided, if known. When using low protein diets one must be careful not to restrict the protein intake to such low levels that protein deficiency occurs. One must take special care when using diets that are deficient in one or more specific amino acids that the restriction is not so severe as to impair protein synthesis.

In some cases of food intolerance it is possible to increase the activity of a deficient enzyme responsible for the food intolerance by the use of a particular nutrient which will cause an adaptive increase in enzyme activity. Since the deficient enzyme is probably defective in structure its activity will not reach normal levels but may increase sufficiently so as to increase the tolerance of the person to the particular offending nutrient. Such an approach has been used in treating sucrase-isomaltase deficiency with fructose[20] and hereditary fructose intolerance and fructosediphosphatase deficiency with folic acid.[24,28-30] It is also important to restrict the foods that contain the offending nutrient. The adaptive increase in the deficient enzymes may give some measure of protection against the inadvertent ingestion of the otherwise toxic nutrient.

The subject of food intolerance is quite complex. Only the broad outline of the subject has been presented here. Clearly, nutrient substances may cause illness so that one can truly say that "One man's meat is another man's poison."

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Diet and Atherosclerosis: Past, Present and Future

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IGNATOWSKI in 1901 and Anitschkow in 1913 induced atherosclerosis in experimental animals by feeding cholesterol enriched diets, thereby initiating more than six decades of work focused on the relationship of diet to atherosclerosis and diet to plasma lipids and lipoproteins.[1,2] As indicated by several recent reviews of the relationship of diet to atherosclerosis and serum lipids, many investigators[3-6] believe that appreciable reduction in the levels of plasma cholesterol and low density lipoprotein cholesterol would ameliorate atherosclerosis or prevent its inception. However, the degrees of certitude relative to these conclusions may differ widely.[3-6]

Irrespective of the controversy about the limitations of the diet-coronary heart disease (CHD) relationship,[3-6] there have been appreciable secular changes in nutritional intake patterns, plasma cholesterol levels and CHD mortality in the last decade. Since 1970 overall dietary intake of cholesterol has fallen and the polyunsaturate/saturate (P/S) ratio of dietary fat has increased.[7-9] Dietary cholesterol intake in children, as well as in adults, appears to be lower than had previously been estimated.[10] Also, within the last decade there has been a downward trend in plasma cholesterol levels.[11] Finally, and perhaps most important, there has been an equitemporal downward trend in CHD mortality.[12,13] In 1975 the reduction in CHD mortality was more than 20 percent overall for persons in the age groups 36 to 74.[12,13] A causal relationship among these aggregate changes in nutritional intake, plasma cholesterol and coronary heart disease has not been unequivocally proven in man. Nevertheless, their equitemporal occurrence leads to speculation[12] that community changes in nutrition might lead to lower plasma cholesterol levels (as shown in the National Diet-Heart Study and in the California three-community studies)[14,15] and, consequently, over time might lead to a reduction in coronary heart disease event rate.

This review will examine data for pediatric and adult populations relevant to the relationship of diet to plasma lipids or atherosclerosis, or both, with the emphasis that a reasoned, data-based, unequivocal resolution of the current controversy "can nutritional diet modification prevent or ameliorate atherosclerosis" is not possible at present.[3-6] Nevertheless, physicians and scientists often must make working decisions in the absence of absolutely conclusive scientific proof.[4] Moreover, after careful assessment of currently available data, three scientific national and representative nutrition councils in the United States have

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ABBREVIATIONS USED IN TEXT

CHD = coronary heart disease
C-HDL = cholesterol carried by high density lipoproteins
C-LDL = cholesterol carried by low density lipoproteins
HDL = high density lipoprotein
LDL = low density lipoprotein
P/S ratio = polyunsaturate/saturate ratio

stressed that reasonable means should be followed to modify the nutritional conditions which contribute to elevated plasma cholesterol and triglyceride levels.[16-18]

In addition, nutritional advisory groups from five other nations have advised that their citizens modify their dietary habits in the direction of lessened intakes of animal and saturated fats.[19] These recommendations have not been made quickly but rather cautiously and over a considerable period (since the early 1960's). Some of the expert committees have been reformed from time to time and yet, after further review of the continually developing evidence, they have reached similar or even firmer conclusions. Where legitimate differences of opinion still yet remain is in the realm of how universally prudent dietary practices should be applied. Should the entire population be advised about dietary change, or only those deemed at risk for the development of coronary heart disease? In the judgments of the American Heart Association and the Intersociety Commission for Heart Disease, dietary prudence is recommended for all.[16,18] However, the Food and Nutrition Board of the National Research Council suggests that only those persons with hyperlipidemia (that is, with plasma cholesterol levels above 220 mg per dl) should change their dietary practices.[17] The surprising degree of agreement is that those with mild to severe hyperlipidemia should restrict saturated fat and cholesterol intakes and observe caloric restriction if overweight. No responsible group of physicians anywhere in this country or elsewhere has advocated no dietary treatment for hyperlipidemia in an attempt to prevent atherosclerosis.

Because hyperlipidemia is such a common condition in this country (a third of adults), it is clear that dietary change at minimum would involve a very large segment of the population and probably millions of families. A nutritional principle which has been applied to the mass fortification of foods with vitamins and minerals is that if the nutritional problem is widely distributed (or could be if not prevented), then it is quite appropriate to recommend that the fortified food be given to all. We suggest that our current epidemic of atherosclerotic coronary heart disease warrants similar consideration. This view receives further emphasis from the next section which deals with atherosclerosis in children.

Diet, Plasma Lipids and Atherosclerosis in Childhood

It is now generally accepted that the genesis of atherosclerosis is in childhood.[20] Coronary and aortic atherosclerosis was reported in a third of soldiers autopsied by Enos and co-workers[21] and McNamara and co-workers[22] and in the youthful years. There is considerable pathologic evidence that the mature fibrocalcific plaque found in middle adult life evolves during the first 20 years.[20-23] There is suggestive, but not unequivocal, evidence that the fatty streak of childhood is a precursor of the mature atherosclerotic lesions.[20-23]

Symptomatic CHD is usually present by the age of 10 and is always manifested in the second decade in children homozygous for familial hypercholesterolemia.[24] In approximately 30 percent of adolescent boys (average age 13), heterozygous for familial hypercholesterolemia, there are abnormal maximum exercise electrocardiographic findings, compared to 7 percent of age-matched normal boys, suggesting the potential of physiologic myocardial ischemia.[25] Also, in young adult men heterozygous for familial hypercholesterolemia, morbidity and mortality from coronary artery disease appears between ages 20 and 30, suggesting that development and progression of the mature atherosclerotic lesions are well accelerated by the end of the second decade.[26] The aggregate data from pathologic anatomical studies,[20-23] and from the most severe manifestations of hypercholesterolemia in children and young adults,[24-26] provide the background that persuades many physicians and scientists that to be effective, prevention of CHD must begin in the teenage years and possibly earlier.[5,20]

Children in the United States have higher plasma cholesterol levels than do children of other populations in which adult atherosclerotic disease is much less frequent.[27-30] Approximately 5 percent of United States children, ages 5 to 18, have plasma cholesterol levels greater than 200 to 220

mg per dl.[27-29] Those children with elevated plasma cholesterol levels in childhood are likely to maintain a similar elevated rank order throughout childhood, into adulthood.[5,29] In addition, children with genetic hyperlipidemia, particularly familial hypercholesterolemia, can be identified in childhood.[29,31]

Childhood Diet and Hyperlipoproteinemia

As summarized by Glueck and Stein,[29] "it is estimated that approximately 1 percent of unselected children have monogenic familial hypercholesterolemia, familial hypertriglyceridemia, or familial combined hyperlipidemia." However, studies in population groups show that most hypercholesterolemia is not due to the "monogenic" familial hyperlipoproteinemias,[31] but is likely related to the intake of dietary cholesterol, saturated fat and total calories.[3-5,31-33] Plasma cholesterol levels in children having low total cholesterol and low saturated fat intake and in vegetarian children are 30 to 40 mg per dl below those of children receiving conventional Western diets.[29,32] Moreover, nutrition modification in small cohorts of children has been shown to produce significant reduction in plasma cholesterol levels. McGandy and associates[34] studied a boarding school population. The calories provided from fat were reduced from 39 to 34 percent. Cholesterol consumption was decreased from 720 to 380 mg per day, and the dietary P/S ratio was increased from 0.2 to approximately 1.2.[34] In 200 schoolchildren, ages 13 to 18, the mean plasma cholesterol level fell approximately 10 percent on this dietary regimen.[34] Using a short-term outpatient protocol in families with adolescent children, Witchi and associates[35] reduced dietary cholesterol and saturated fat, and increased polyunsaturated fat. An average reduction in serum cholesterol approximating 10 percent was produced in adolescents over three weeks.[35] There was a high degree of dietary cooperation among the free living families in this study.

In a longer-term study in younger children, Friedman and co-workers[36] provided low cholesterol, low saturated fat diets to normal infants from birth. At age 3, their mean cholesterol levels were 145 ± 4 mg per dl, significantly lower than in 422 controls whose mean values were 154 ± 1, having had no dietary intervention.

Stein and associates[37] evaluated 229 adolescent males in a South African boarding school. The type of dietary fatty acids was altered, but not the amount of total fat or cholesterol. Using polyunsaturate-rich, saturate-poor diets, a 14 percent reduction in total and low density lipoprotein plasma cholesterol was achieved. The final ratio of polyunsaturate to monounsaturates to saturated fats was approximately 1:1:1.

The above findings[34-37] suggest that prudent, and relatively easy-to-achieve dietary changes, similar to those suggested by various nutritional councils,[16,17] would be successful in lowering plasma cholesterol levels in American children. Such diets would be particularly effective in that majority of children whose hypercholesterolemia was secondary to excessive ingestion of cholesterol and saturated fat.[29,37]

Dietary modification also has considerable utility in children who have familial hypercholesterolemia or hypertriglyceridemia, or both. Approximately a third of children with familial hypercholesterolemia will attain normal total plasma cholesterol and low density lipoprotein (LDL) cholesterol levels with dietary modification which reduces fat to 25 percent to 30 percent of total calories, substitutes polyunsaturates for saturates to reach a P/S ratio of 1:1 and limits dietary cholesterol to less than 200 mg per day, adjusted downward for younger children.[5,29] Above age 10 in children heterozygous for familial hypercholesterolemia[5,29] such a diet may reduce total and LDL cholesterol by 10 percent to 20 percent, but will not usually bring plasma cholesterol to normal levels. Therapy with bile acid binding resins is often necessary in such children to attain adequate control.[5] Elevated triglycerides in most children with familial hypertriglyceridemia can be brought to normal levels by weight reduction.[5,29]

Epidemiological[3-5,16,32] and pathological[20-23] evidence in humans and evidence from experimental animals suggests that maintenance of low plasma cholesterol levels beginning in childhood might be much more effective in retarding the progression of atherosclerosis than reducing levels beginning in the fourth or fifth decades.[5] A controlled and blinded test to this hypothesis has not and probably never will be done due to overwhelmingly expensive logistics and the necessity for a four to five decade follow-up if the study begins in the first decade of life.[5] Although opinion is widely divided about the advisability of recommending a modified diet for all children,[29] there is near unanimity that children falling in the

top decile of their age and sex distribution for plasma cholesterol and triglyceride levels should be treated.[5,29,35]

Diet-Atherosclerosis Relationships in Adults

Three decades of detailed epidemiological studies have identified major risk factors for CHD including age, sex, hypercholesterolemia (elevations of LDL cholesterol), hypertension, cigarette smoking and diabetes.[3-6,38-40] Obesity, personality type and lack of physicial activity are additional, but less well-established risk factors.[3-6,38-40] These established risk factors "may be causal agents, intervening variables, or secondary indicators of a more fundamental disturbance."[5] The amounts of cholesterol carried by the low density lipoproteins and by the high density lipoprotein (HDL) are more specific and have opposing risk factors for CHD (positive for C-LDL, inverse for C-HDL).[41,42]

Recommendations for dietary modification in population groups[16] blanket a heterogeneous group of subjects whose CHD risk status could be better gauged individually by measurement of fasting plasma cholesterol, C-HDL and triglyceride, allowing estimation of C-LDL.[4,5] Specific lipoprotein sampling would facilitate identification of the approximately one out of 250 unselected Americans[29] with familial hypercholesterolemia, who usually require individually determined diet and drug treatment.[24-26,29] The approximate 30 percent of Americans having total plasma cholesterol levels of 250 mg per dl or greater would also be identified,[43] a group of subjects shown to be at sharply increased CHD risk.[43] Since CHD risk increases along with total plasma cholesterol throughout its entire distribution,[39,40] (one basis for population-wide dietary modification recommendations),[14,16] specific lipoprotein measurement would locate persons within the distribution.

As is the case for children, hypercholesterolemia in adults is probably for the most part not due to the familial hyperlipoproteinemias,[29,31,33] or to polygenic traits, but is most likely related to the intake of dietary cholesterol, saturated and polyunsaturated fat, and total calories. Moreover, in adults the development, progression and potential regression of the atherosclerotic lesion appears to be closely related to the plasma cholesterol level.[6,43-47]

Connor and associates and Mattson and associates have shown[48,49] that dietary cholesterol has a close correlation with plasma cholesterol levels over a dietary range of 0 to 600 mg per day, but a further increase above 600 mg per day does not further substantially increase plasma cholesterol levels.[48,49]

Over a 20-year period of study, Keys and coworkers[50,51] have shown that increments in dietary saturated fatty acids elevate serum cholesterol levels, whereas polyunsaturated fatty acids tend to diminish them. Mattson and associates[52] found that sharp increments in trans fatty acids in the diet (present in partially hydrogenated vegetable oils) had no specific effect on plasma cholesterol and triglyceride.

Studies in vegetarians and primitive people whose dietary cholesterol, saturated fat and total calorie intake is sharply lower than that in Westernized societies, have suggested overall a significant relationship among diet, plasma lipid levels and coronary heart disease.[53-55] Keys and associates[56] have shown, in Japanese migrants to Hawaii and California, a close and consistent relationship between dietary saturated fats, blood lipids and CHD event rates.

Dietary modification in specific small cohorts can significantly lower serum cholesterol levels,[6,14,44-47,48,49] particularly when accompanied by a reduction of cholesterol and total saturated fat intake, and a relative increase in polyunsaturated fats.[57] Weight reduction and modification of dietary lipids may well have a synergistic effect.[58]

Despite the incremental evidence relating dietary cholesterol and saturated fat to CHD there are clearly areas of discordance.[6] Within culturally homogeneous groups, epidemiologic studies in children and adults may at times (as in the Tarahumara Indians) but not always show significant associations between nutrient intakes and serum lipids[10,32,59] or CHD risk.[59] There are certain limitations to the interpretations of such studies.[60] Random errors in the collection of dietary data would lead to the underestimation of any relationships between nutrients and CHD.[60] Moreover, recent diet habits do not represent lifetime patterns, and development of atherosclerosis over decades makes it misleading to relate recent dietary practices to the risk of CHD.[3-5]

A more serious challenge to believability of the diet-heart relationship has been the lack of unequivocal, uniform reduction in "hard" or "soft" end points in populations where diets have been modified[44-46,61] or where lipid-lowering drugs have been given.[62] In four dietary modification trials completed, there was significant lowering of plasma cholesterol, and suggestive but not un-

equivocal reduction in "hard" and "soft" end points for CHD.[44-46,61] The drug-heart study did not systematically utilize dietary modification.[62] Using nicotinic acid and clofibrate (Atromid), there was no conclusive reduction in CHD morbidity and mortality after five years of followup.[62] These small clinical trials may (speculatively) have failed to detect a substantial effect on CHD because they were carried out in adults whose atherosclerosis was advanced and potentially irreversible.[44-46,61,62] A controlled trial on the effect of dietary modification on CHD in young adults is probably not feasible,[14] due to the requirement for an unmanageably large number of subjects in order to obtain statistically convincing results. There are, however, two very large intervention trials currently underway. It is hoped that the MRFIT trial (modification of diet, smoking and hypertension) and the Lipid Research Clinic (LRC) study (modified diet and cholestyramine resin) will provide incremental evidence relevant to amelioration and prevention of CHD in adults.

Results from the MRFIT and LRC studies probably will not become available until 1983 or later, and will necessarily be primarily applied generally to a truncated segment of the population distribution selected by virtue of high initial risk. Studies in the future might profitably focus on the essentially unexplored relationships of C-HDL to diet, and to other environmental factors. Since studies designed to lower total plasma cholesterol and C-LDL have provided only reduction in CHD in selected groups of the population[44-46,61,62] or cases of total vascular disease,[44-46,61,62] safe and effective methods to elevate C-HDL might open up alternative avenues to amelioration of atherosclerosis. Careful epidemiological studies of the secular trends towards reduction in dietary cholesterol and saturated fats, plasma cholesterol and CHD event rates should be continued and expanded, perhaps to include prospective cohort follow-up, to identify, if possible, any etiological relationships between these variables. Further assessment and documentation of the possible CHD-sparing effects of balanced exercise programs,[63] and their long-term relationship to plasma lipids and lipoproteins may be an exciting and underevaluated area for future work.

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Metabolic Effects of Dietary Fiber

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DIETARY FIBER has been defined as plant material that is not digested by enzymes of the human gastrointestinal tract. The plant materials that we call fiber are the structural components of plant cell walls. The amount and type of this material vary widely over the plant kingdom but can be broadly subdivided into polysaccharides (cellulose and noncellulosic polysaccharides) and lignins. These materials differ from one plant to another and may vary in the same plant, being affected by age and environment. The cellulosic materials form cellules and fibrils; the gums and mucilages form the cement substance of cell walls and seeds, and the woody material is a complex, cross-linked phenylpropane polymer, lignin.

Cellulose is a linear homoglycan composed of a chain of glucose residues in a 1-4 β linkage. The noncellulose types of polysaccharide are branched chain materials containing a number of different sugars. Hemicellulose has a main chain containing xylose, mannose, galactose and glucose with side chains of arabinose, galactose and glucuronic acid. Galacturonic acid represents the main chain of pectic substances whose side chains contain rhamnose, arabinose, fucose and xylose. The principal chains of gums and mucilages are more complex, the former containing galactose, galacturonic acid-rhamnose and glucuronic acid-mannose and the latter galacturonic acid-rhamnose, arabinose-xylose, glucose-mannose and galactose-mannose. The side chains of mucilages and of algal polysaccharides contain only galactose, whereas side chains of gums contain xylose and fucose as well as galactose. The main chains of algal polysaccharides contain mannose, xylose, guluronic acid and glucose. Lignin is a polymer of sinapyl, coniferyl and coumaryl alcohols. Cell walls also contain proteins, phytic acid, silica, tannins, steroid glycosides and cutins, which are polymeric esters of fatty acids.

Until recently, the only measure of fiber content was a 150-year-old method involving treatment with acid and alkali. The residues left after these treatments were grouped together as crude fiber. This fraction represented only cellulose and lignin and did not account for any of the variety of other substances. At this writing most published data for fiber content of food are given as crude fiber. Van Soest[1] has developed a system in which aliquots of material are treated with a neutral solution of detergent or an acidic detergent solution. The former treatment yields total cell wall constituents and the latter cellulose and lignin. Treatment with strong (72 percent) sulfuric acid at room temperature yields lignin only. The system permits calculation of cellulose content by difference. Southgate[2,3] has developed a complex method, involving enzymatic hydrolysis plus other hydrolysis and extraction procedures, which yields much more comprehensive information. Southgate[4] has analyzed a number of foodstuffs. His analysis shows the wide gap between total dietary fiber as determined by Southgate and crude fiber as determined by the older standardized method and quoted in the United States Department of Agriculture's Handbook 8,[5] which is virtually (and deservedly) the bible of nutritionists. To give a few examples: the total dietary fiber content (grams per 100 grams) of broccoli, peaches, peanuts and cocoa powder is 4.1, 2.3, 9.3 and 43.3, respectively; their crude fiber content is 1.5, 0.6, 2.4 and 4.3. With introduction of the Van Soest and Southgate methods more accurate information concerning the true composition of dietary fiber is forthcoming. Such infor-

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mation is necessary to understand better the physiological effects of fiber.

The effect of fiber on laxation was known to Hippocrates (quoted in reference 6). Cowgill and co-workers[7,8] and Williams and Olmstead[9] described the laxative effects of bran and other foods such as cabbage and cereals. Williams and Olmstead[9] were not able to correlate laxative effects with composition. Burkitt[10,11] noted rapid transit time and increased stool weight in African children on a high residue diet compared with English school boys. Not all fiber is effective in this respect; agar and psyllium seed colloid are the bases of commercial laxatives. Wheat bran is particularly good for decreasing transit time and increasing frequency of defecation and stool bulk. Addition of 16 grams of bran to the daily diet can double fecal weight.[12] On the other hand, pectin[13] and lignin[14] have little effect on transit time or stool bulk.

Fiber is resistant to enzymes of the alimentary tract but can be digested by bacterial enzymes. This breakdown occurs in the colon and 30 percent to 80 percent of cellulose and 55 percent to 85 percent of hemicellulose can be lost in this way.[15-18] About 90 percent of pectin is digested[19,20] but only 30 percent or less of wheat bran is,[21] and practically no lignin is digested.[16,18]

Fiber degradation produces hydrogen, carbon dioxide, water, methane and C_2-C_4 fatty acids. These products can also act to increase laxation.[22]

Diverticular Disease

Based on their observation of the large difference in incidence of diverticulosis in Western countries and African countries, Painter and Burkitt[23] postulated that a low fiber diet resulted in high colonic pressure and the appearance of diverticulae.

In the past, a low residue diet was recommended in diverticular disease,[24,25] but today the reverse is being suggested. Bran has been found to be very effective in treatment of this condition.[26-29] Painter and co-workers[27] fed 3 to 45 grams of bran daily (mean 13 grams) to patients with diverticular disease and found relief of symptoms in 83 percent. There is little information on the treatment of diverticular disease by using fiber other than bran. Fiber is also being used in treatment of irritable bowel syndrome.[30]

Cancer of the Colon

There are two currently popular hypotheses regarding diet and the cause of cancer of the colon. Burkitt[31-33] has pointed out that cancer of the colon is rare in populations subsisting on high residue diets. He has postulated that the lack of fiber in the Western diet permits greater exposure of the lining of the colon to carcinogens that may be present in feces and the slower transit time allows more time for bacterial transformation of dietary or secretory material to possible carcinogenic agents. Drasar and Irving[34,35] have found little correlation between dietary fiber and cancer of the colon but found high correlation of cancer of the colon with ingestion of animal fat and animal protein. There is a parallel between standard of living, Westernization of the diet and incidence of cancer of the colon.[36-38]

It might be of interest to digress for a moment and discuss other aspects of diet and cancer of the colon. Stavraky[39] has pointed out that the intranational differences in cancer of the colon found in countries such as the United States, Scotland and Canada lend no support to a theory involving specific dietary components. Although the consumption of beef in the United States doubled between 1945 and 1970, the death rate from cancer of the colon was unchanged.[40] Within the United States, mortality from cancer of the bowel is highest in the Northeast and lowest in the Southeast.[41] The diet in these two regions is not remarkably different. Populations such as Seventh Day Adventists who are largely vegetarian and who eschew pork have a low incidence of colon cancer,[42] but so do Mormons[43] who eat meat regularly. Clearly there is still much to be elucidated here.

Experiments with animals have shown that some types of fiber can protect against induced colon cancer. More than 20 years ago it was found that rats fed stock diets exhibited fewer 2-acetylaminofluorene-induced tumors than did rats fed semipurified diets.[44,45] Wilson and associates[46] and Fleiszer and co-workers[47] reported that dietary bran protected against tumors induced by dimethylhydrazine. Watanabe and co-workers[48] tested several dietary fibers for their effect on appearance of tumors of the colon caused by injection of dimethylhydrazine or intrarectal instillation of azoxymethane. Bran had little effect, pectin offered some protection and alfalfa enhanced tumor incidence. Alfalfa has been found to denude the colonic epithelium[49] which may explain the findings. Barbolt and Abraham[50] have found bran to protect rats from

colonic tumors caused by feeding of dimethylhydrazine.

The data suggest that the effects of fiber in experimental colon carcinogenesis vary depending on the type of fiber used and the mode of administration of the carcinogen. Insofar as the question of diet and cancer of the colon in man is concerned, it would appear as if a few pieces of the jigsaw puzzle are still missing.

Gallstones

Dam[51,52] has reviewed factors that affect gallstone formation. Gallstones can be induced in hamsters by feeding a diet containing 74 percent glucose, 20 percent casein, salt mix, vitamin mix and choline chloride. The diet need not contain either fat or cholesterol. Replacement of the glucose with rice starch reduces gallstone formation almost to zero. Bergman and van der Linden[53] fed this type of diet to hamsters and augmented it with 5 percent pectin, lignin or psyllium colloid. None of the hamsters fed lignin or psyllium were found to have gallstones, 29 percent of those fed pectin had gallstones, whereas 58 percent of the controls had gallstones. Gallstones formed in mice fed a lithogenic diet were dissolved when the mice were returned to laboratory ration.[54] Rabbits fed a semipurified diet containing 30 percent casein and 15 percent beef tallow exhibited gallstones (3/5) but when 5 percent pectin was added to the diet no gallstones were observed.[55]

It has been suggested that a diminished bile acid pool plays a role in cholelithiasis in man.[56-58] Nigerians ingesting a high fiber diet have increased bile acid pool size and increased bile acid synthesis rates compared with populations eating a "Western" diet.[59] Pomare, Heaton and associates[60] showed that when patients with gallstones were fed wheat bran (an average of 57 grams per day) their chenodeoxycholic acid pool increased significantly, the deoxycholic acid pool fell and the cholesterol saturation of their bile diminished.

The mechanism of action of fiber in affecting cholelithiasis is unknown, but it may be related to the increases in bile acid pool size that have been observed in rats[61] and monkeys.[62]

Lipid Metabolism

The influence of dietary fiber on lipid metabolism and atherosclerosis has been the subject of several recent reviews.[63,65]

A review of the literature relating to the effect of saturated fat on atherosclerosis in rabbits showed that the fat was atherogenic only when fed as part of a semipurified diet.[66] It was further shown[67,68] that addition of coconut oil to the fat-free residue of commercial rabbit ration was not atherogenic. Moore[69] added wheat straw to a semipurified, cholesterol-free atherogenic diet and showed that serum lipid levels and atherosclerosis were much lower than those of rabbits fed cellulose or cellophane.

Cellulose is ineffective in lowering cholesterol levels of rats[70-72] or rabbits.[73] Pectin and lignin, on the other hand, are hypocholesteremic in these species.[73-77] Pectin inhibits atherogenesis in chickens.[78]

In rats fed a variety of starches in diets containing cholesterol and hydrogenated peanut oil there was an inverse relationship between the fiber content of the starch and accumulation of cholesterol in serum, liver and aorta.[79]

Fiber plays some role in bile acid metabolism. Portman[80] reported that rats fed a semipurified diet excreted a smaller quantity of steroids than did rats fed commercial ration. Leveille and Sauberlich[74] reported that rats fed pectin in a diet containing cholesterol excreted more bile acid but no more neutral steroid than did controls. A number of investigators have shown that dietary fiber along with other ingredients of the diet can bind appreciable quantities of bile acids and bile salts.[81-87] This action may be important in assessing the mode of action of fiber but more data are needed.

Vegetarians ingest more fiber than do persons eating a mixed diet, and they have lower cholesterol levels.[88-89] Bran has been used extensively as a dietary source of fiber but with one exception[90] has been found to have no hypocholesteremic effect.[91] Pectin[13,92-96] fed at levels of 6 to 50 grams per day has a hypocholesteremic effect in man. Pectin results in a large increase in bile acid excretion and a smaller one in neutral steroid excretion.[13,96] Guar gum (6 to 36 grams per day) also has a hypocholesteremic effect.[94,97] Antonis and Bersohn[98] found that the level of fat in the diet affected excretion of steroids in the feces; therefore, on a low fat-high fiber diet excretion of both acidic and neutral steroids was increased, but on a high fat diet fiber only affected neutral steroid excretion.

Grande[99] summarized data on a number of studies in which dietary sucrose was replaced equicalorically by starch (as bread, legumes, fruit

and the like). A fall in serum cholesterol levels was noted in every study. The foods containing starch contained varying amounts of fiber.

Dietary fiber has been shown to improve glucose tolerance. The materials tested have been pectin, guar and bran.[100-103] Kiehm and co-workers[103] fed diabetic patients a 2,200 calorie diet in which about 75 percent of the calories were present as carbohydrate, two thirds as complex carbohydrate. Serum glucose, triglyceride and cholesterol levels fell by 26 percent, 15 percent and 24 percent, respectively.

Ingestion of fiber is not without hazard. Increase in volatile gas in the large intestine can lead to sigmoid volvulus, a twisting of the large intestine. This condition has been found to be more prevalent among populations ingesting a high fiber diet.[104] High fiber diets, especially those containing phytate, may decrease bioavailability of necessary divalent cations.[105-108] Some types of fiber contain inhibitors of trypsin and chymotrypsin which could influence digestion and be deleterious in persons ingesting marginally adequate diets.[109,110]

Beneficial effects from increased dietary fiber have been claimed for a wide spectrum of diseases. The two that have received the most attention, heart disease and cancer, are diseases whose causes are still unclear. To compound the confusion, fiber is a generic term covering a variety of complex structures with different chemical and physical properties. Still, dietary fiber may be effective in treating some aspects of these diseases. What needs to be learned is the mechanism or mechanisms of action involved in the hypocholesteremic and antiatherogenic effects of certain types of fiber. The same is true for the much smaller area of work involving effects of fiber in carcinogenesis. Realistic dietary recommendations depend upon elucidation of the modes of action of fiber.

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Obesity: Fat Cells—Not Fat People

New Therapeutic Goals

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AMONG AFFLUENT technically developed societies, an abundance of high caloric foods is conveniently available in tempting variety. This circumstance, coupled with a wide proliferation of labor-saving devices, has resulted in progressive increases in the endogenous storage depots of fat among greater numbers of children as well as adults. Practical methods to assess the degree of "fatness" among these patients have generally been less than satisfactory. Direct techniques to estimate lean body mass and total body fat are not convenient enough for routine clinical use. Accordingly, physicians have tended to rely on indirect measurements such as skin-fold thickness,[1] various indices of body weight[2,3] or, more commonly, biodata tables published by insurance companies.[4]

With this last criterion, current estimates suggest that as much as 30 percent of the United States population exceeds what is termed ideal weight* by 20 percent or more[5]—the relative weight generally accepted as defining obesity.[6]

Unfortunately, these direct or indirect methods fail to estimate the total number of adipose cells within which total body fat is distributed. Because metabolic abnormalities such as insulin resistance, hyperlipidemia and hyperglycemia correlate primarily with the enlargement of adipose cells rather than with their number or total body fat,[7,8] valid reasons exist for reevaluating the definition of obesity. In this article an attempt is made to redefine obesity on the basis of new information concerning developmental, structural and physiological characteristics of the adipose organ as well as upon data relating to epidemiological aspects of its relation to coronary risk. Evidence will be reviewed refuting the prevailing general definition of obesity as an excessive amount of total body fat and supporting a more precise definition of obesity as *an excessive amount of fat per adipose cell.*

The Adipose Cell Theory

Evidence for Two Major Forms of the Obesity Syndrome

The concept of two major forms of clinical obesity is based on the following reported observations of Hirsch and co-workers[9,10] and Björntorp and co-workers.[11,12]

Normal Adiposity

The number of adipose cells in adults is constant whether weight increases[13] or decreases.[9] Patients of normal insurance-table weight average about 26×10^9 cells, which contain about 25 to 35 pounds of total body fat. For example, a normal man with a height of 68 inches would weigh approximately 68 kg (150 pounds), of which 54.4 kg (120 pounds) is the lean body mass and 13.6 kg (30 pounds) consists of fat (Figure 1). Since 13.6 kg represents approximately 14×10^9 μg, the average quantity of fat per cell is, therefore, approximately 0.6 μg per cell.

Hypertrophic Obesity

Patients with adult-onset obesity have the normal fixed number of fat cells. Therefore, the extra 13.6 or 27.2 kg (30 or 60 pounds) of fat is dis-

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*Ideal weight is arbitrarily selected as an average weight of a 25-year-old person of similar sex, height and estimated body-frame size.

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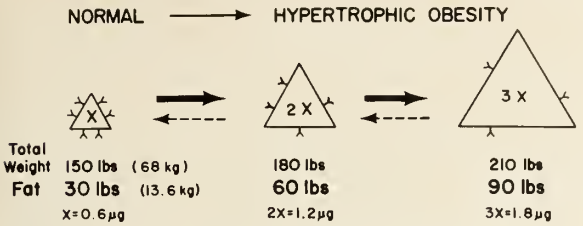

Figure 1.—Characteristics of normal and hypertrophic adipocytes. >—— represents insulin receptors on cell membrane; X represents the average triglyceride content of the normal fat cell.

tributed within their 26×10^9 cells, resulting in enlarged or hypertrophied cells containing an average of 1.2 μg or 1.8 μg of fat per cell, respectively (Figure 1).

Hyperplastic-Hypertrophic Obesity

During childhood, all cells of the body, including the adipose tissue, are able to grow in number as well as size. Adults whose obesity developed in childhood are observed to have an increased number of fat cells as well as increased fat per cell. Indeed, they are reported to have two to four times the normal number of adipose cells with each averaging two or three times the normal fat content.[8,10] Consequently, instead of a normal amount of total body fat (13.6 kg, 30 pounds), they have from 54.4 to 122.4 kg (120 to 270 pounds) of fat, making a total body weight of 108.8 to 176.9 kg (240 to 390 pounds). This type of obesity is characterized as mixed hyperplastic-hypertrophic (see Figure 2).

Fat-Cell Weight Versus Insurance-Table Weight

When a hypertrophic adult-onset obese person reduces to normal fat-cell weight of approximately 0.6 μg per cell, he has also reached the normal insurance-table weight since the number of fat cells in adult-onset obese patients is normal. In contrast, when the hyperplastic-hypertrophic obese patient decreases his weight during inpatient caloric deprivation or after a jejunal-ileal bypass operation, the amount of fat per cell would reach normal quantities long before insurance-table weight is achieved. Therefore, when the patient has reduced to 81.6 kg (180 pounds), the 27.2 kg (60 pounds) of total body fat is distributed within twice the normal number of cells so that there is pure hyperplasia of the adipose tissue without hypertrophy (Figure 2). At this point, despite

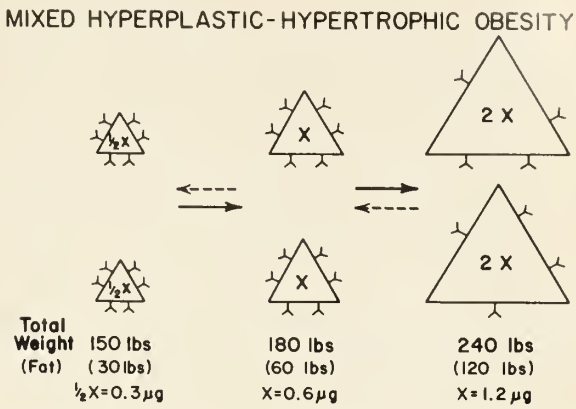

Figure 2.—Comparison of adipocytes in mixed hyperplastic-hypertrophic obesity at various levels of body weight (see Figure 1 for symbols).

total body fat being twice normal and insurance tables depicting a weight reaching 20 percent over the "ideal," the patient should not be considered pathologically obese because the amount of fat *per adipose cell* is normal and correlations with metabolic dysfunction have not been found when cell size is normal.[7,8]

Technical difficulty in obtaining adequate biopsy specimens of fat tissue from undernourished patients has resulted in inadequate data among thin patients. While all thin patients have reduced total body fat by definition, the adipose cell theory implies that adult-onset thinness would consist of the normal number of cells with hypotrophic adipocytes (for example, in anorexia nervosa developing after the age of 20). In contrast, undernourished children would have hypoplastic adipose tissue that could conceivably contain either normal quantities of triglyceride (if the undernourishment is treated) or hypotrophic cells as well. Therapy directed at restoring the hypotrophic cells to normal size would, in the case of the adult-onset form, produce a normal insurance-table weight. In contrast, among the childhood-onset type with hypoplasia, correction of the hypotrophic adipocytes would occur at a weight considerably less than that depicted as normal on insurance tables.

Some Metabolic Consequences of Hypertrophic Obesity

The circulating hormone insulin is particularly responsible for promoting as well as maintaining neutral fat within adipose tissue. A number of other hormonal and neural substances modulate this storage action of insulin by mobilizing these energy depots at times of caloric need. To initiate

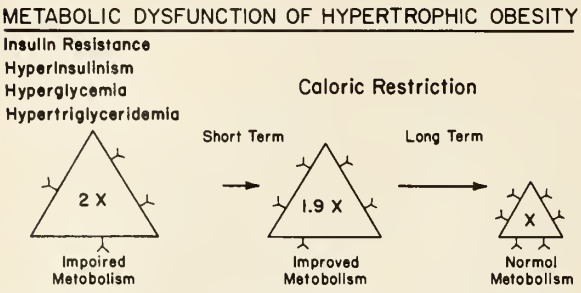

Figure 3.—Restoration of insulin receptor concentration and correction of metabolic dysfunction in hypertrophic obesity after caloric restriction and weight reduction to normal triglyceride content of adipocytes (see Figure 1 for symbols).

its hormonal effect of clearing ingested foodstuffs from the blood and promoting and maintaining their storage, insulin binds to specific membrane receptors present on various target organs for insulin, including the adipocyte.[14,15]

Generally, obese patients are relatively insensitive to the action of insulin and require exaggerated insulin levels to clear a glucose load.[16]

Recent studies have emphasized that this insulin insensitivity and hyperinsulinism with their associated delayed clearance of glucose and triglycerides *in vivo* correlate primarily with fat-cell size rather than with either fat-cell number or total body fat.[7,8,17] Similarly, measurement of insulin-binding to receptors on the surface of adipocytes has shown there to be decreased binding only in hypertrophic adipose cells but not in normal-sized adipocytes.[15] This observation could explain those occasional patients with childhood-onset obesity in whom hyperinsulinism is minimal or absent and insulin-binding to fat cells is not decreased despite a pronounced excess of total body fat.[15,18] Fasting and postprandial hyperglycemia are quite rare in obese children, as compared with obese adults who often have mild degrees of diabetes mellitus. One protective factor in this regard may be the ability of adipocytes to replicate during childhood in response to overfeeding, thereby minimizing hypertrophic changes.

Adults with predominantly hyperplastic obesity are rare because, presumably, the stimulus to develop hyperplastic adipose tissue is associated with overfeeding, which continues to produce excess fat as adipocytes mature to the adult nonreplicating form. When hypertrophy is present, whether accompanying the normal number of cells (Figure 1) or associated with hyperplasia, a number of metabolic cardiac risk factors appear which improve with caloric restriction and disappear once weight reduction corrects the hypertrophy (Figure 3).

While the exact mechanism of insulin-resistance in hypertrophic adipocytes is not clear, it appears that an overdistended fat cell may directly resist further entry of glucose and triglycerides because of intrinsic regulatory mechanisms. In addition, the associated hyperinsulinemia results in "down-regulation" of insulin receptors. Figure 3 shows the short-term effect of caloric restriction, wherein a reduced stimulation of beta cells results in reduced circulating insulin levels. This ameliorates "down-regulation" of receptors, which thereby partially restores the concentration of insulin receptors on the surface of the fat cell. With further weight reduction, the normal-sized adipocyte regains its normal responsiveness to insulin and is no longer associated with elevated levels of circulating glucose, triglycerides or insulin.[19,20]

Identifying Type of Obesity and Relevance to Prognosis

At present, techniques for accurate fat-cell sampling, cell counting and quantification of triglyceride content are complicated and seldom available clinically. In addition, numerous biopsy studies may be required to characterize fat-cell morphometry accurately in a single patient. One group has reported as much as 100 percent variation in cell size during consecutive sampling from adipose tissue in the same patients.[21] From the foregoing comments, it is obvious that a vigorous research effort to develop improved morphometric methods would be most worthwhile. Meanwhile, reliance on certain clinical features of obese patients may assist in the differentiation: Those patients with a childhood history of obesity, characteristically centrifugal in distribution, and who weigh more than 113 kg (250 pounds) are most likely to be hyperplastic-hypertrophic types;[22] those who develop more of a centripetal type of obesity, occurring after adulthood, and who weigh less than 90.7 kg (200 pounds) are less likely to be hyperplastic.[22] A clinical indicator of fat-cell hypertrophy in either obese group would be the presence of hyperinsulinism, impaired carbohydrate tolerance and hypertriglyceridemia.

From the epidemiological standpoint, risk of myocardial infarction primarily relates to metabolic consequences of obesity, such as hyperlipidemia and hyperglycemia, rather than to the obe-

sity itself.[23,24] Since these factors relate particularly to fat-cell size, this suggests a medical indication for therapy only when the fat cell is enlarged. There is no known treatment for excessive numbers of fat cells, and, if they are of normal size, they should not disturb metabolic measurements despite their association with increased total body fat. Attempts to reduce total body fat to an insurance-table norm in patients with increased numbers of adipocytes are extremely difficult, possibly because the resultant semistarved condition of individual fat cells induces compensatory forces stimulating appetite as well as reducing basal metabolic rate. Also, insulin-receptor concentration may conceivably increase to supranormal quantities in the shrunken adipocyte. All of these responses would lead toward restoring fat within the reduced fat cell. If these normal compensatory mechanisms are forcibly suppressed, physical disability and psychological depression are likely to occur, as reviewed by Stunkard and associates.[25] Their evidence included the Rockefeller University report that, after 16 weeks of inpatient dieting in ten patients with childhood-onset hyperplastic-hypertrophic obesity, severe psychological depression developed as their total body fat approached normal, but in five adult-onset obese patients there was an enriched sense of well-being when body weight was brought to normal levels.[26]

While these hyperplastic-hypertrophic patients have metabolic features of insulin resistance that clear when they reach a normal fat-cell weight, their excess of total body fat in the pure "hyperplastic" phase may continue to produce mechanical consequences such as arthritis of weight-bearing joints, breathing difficulty and greater postsurgical risk. Advantages of further weight reduction to improve these mechanical problems must be balanced against the possible psychological disadvantages and high failure rate of attempting to reduce adipocytes below their normal weight.

Redirection of Therapeutic Goals in Obesity

Therapy in obese patients is difficult enough without compounding the problem by indiscriminately grouping together two quite different clinical types. The more common hypertrophic, adult-onset obese patients generally have a more favorable prognosis for successful reduction to, and maintenance of, insurance-table ideal weight. This is in pronounced contrast to the hyperplastic-hypertrophic patients in whom normal insurance-table weight is seldom achieved and virtually never maintained, despite repeated attempts to achieve this elusive goal.

For hyperplastic-hypertrophic patients, a more realistic aim is the elimination of their fat-cell hypertrophy to minimize the metabolic consequences of obesity, particularly hyperglycemia, hyperinsulinism and hyperlipidemia. Reduction of fat-cell numbers with present day techniques is as impossible as reducing body height or bone structure. Previous goals that did not consider cell number led to deterioration of self-concept and recurrent depression consequent to repeated futile attempts to reach and maintain a state of cellular starvation. Unfortunately, the therapy for obesity as reported in publications from university medical centers, practicing bariatricians or weight-reducing organizations has concerned itself mainly with the more conspicuous hyperplastic-hypertrophic obese patients. Presumably, their greater body mass as well as their refractoriness to weight reduction have resulted in their disproportionate concentration in these treatment centers, and the literature therefore emphasizes the high failure rate in achieving or maintaining ideal weight in obesity. As a result, the much more prevalent type of patient with adult-onset hypertrophic obesity has often been deprived of the metabolic and cardiovascular benefits of an energetic, intensive program of weight reduction because of this aura of "failure" associated with treatment of a different form of obesity.

It is hoped that awareness of the significance of adipose cell number and size will alleviate this tendency to nihilism and help redirect therapeutic goals in a more realistic and achievable manner.

Summary

Evidence exists for two distinct forms of the obesity syndrome, and enlarged "hypertrophic" adipocytes are common to both. It is their number that distinguishes each form: A normal number of fat cells characterizes adult-onset hypertrophic obesity; an increased number, the childhood-onset hyperplastic-hypertrophic type. In both, fat-cell hypertrophy accounts for the observed metabolic sequelae, including insulin insensitivity, hyperinsulinism, hypertriglyceridemia and delayed glucose clearance—all of which contribute to an increased cardiovascular risk. In those rare patients with excessive quantities of total body fat in whom

these metabolic features are normal, predominant hyperplasia is suggested.

Until improved techniques of adipocyte morphometry are available, therapeutic goals in managing obesity should be directed primarily at reducing the circulating levels of insulin, triglycerides and glucose to normal. With adult-onset hypertrophic obese patients this will coincide with attainment of normal insurance-table weight. By contrast, in hyperplastic-hypertrophic obese patients, normalization of these metabolic features occurs long before insurance-table weight is achieved.

Failure to consider these differences among patients categorized as obese based on indirect measures of total body fat has resulted in considerable frustration, unnecessary psychological despondency and a profoundly debased self-concept in patients with hyperplastic-hypertrophic obesity. An additional consequence has been the unfortunate presumption of hopelessness in treating adult-onset hypertrophic obese patients, leading to a lack of enthusiasm and motivation in both patient and therapist.

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Zinc Metabolism and Its Implications in Clinical Medicine

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DISTURBANCES IN ZINC HOMEOSTASIS are being reported in increasing numbers. Concomitantly "nutritional support" with zinc and other vitamin and mineral supplements is currently being advertised as adjunctive treatment in conditions where dietary intake has been inadequate. Some examples include conditions such as alcoholism, major burns, prolonged infections, massive trauma and repeated surgical interventions. Furthermore, within the past five years, two separate disorders of zinc metabolism have been recognized[1,2] and the standard American diet has been calculated to be on occasions marginal or deficient in zinc.[3]

Studies in humans presently indicate that zinc is needed for achievement of normal growth, for normal sexual maturation and function, and for maintenance of a normal appetite and taste acuity. Wound-healing, normal psychocognitive function and preservation of the integrity of epithelial surfaces also depend on an adequate nutritional intake of zinc.

Zinc is a trace element—that is, an element that forms less than 0.01 percent of the body weight—whose essentiality as a nutrient for mammals was discovered more than 40 years ago. Because this metal is fairly ubiquitous, human deficiencies of nutritional origin were considered improbable. In 1961, however, Prasad suggested that a syndrome of dwarfism and hypogonadism, seen in adolescents in Iran, might be caused by a nutritional deficiency of zinc,[4] and attention was drawn to the possibility of zinc deficiency in man.

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In this article, pertinent aspects of zinc metabolism and biochemical functions in humans will be reviewed, with reference, when necessary, to animal studies. The disease states in which zinc supplementation may be useful will then be discussed.

Body Content and Distribution

The total body content of zinc in a hypothetical 70-kg (154-pound) man approximates 2.5 grams, with 30 percent of the total zinc present in bone and 60 percent in muscle. The highest concentrations occur in eyes, hair, male reproductive organs and bone. Intermediate levels are present in liver, kidney and muscle (Table 1). In blood, 80 percent of the zinc is found in the erythrocytes, mainly as red blood cell carbonic anhydrase. Plasma zinc levels range from 70 to 110 μg per dl, serum zinc levels are approximately 10 percent higher. The normal range of plasma zinc concentrations varies, consequently it is important to know each particular laboratory's range before deciding if a patient has hypozincemia. Of the plasma zinc, approximately 50 percent is freely exchangeable, being loosely bound to albumin. Another 7 percent is amino-acid bound, mainly to histidine and cysteine. The remaining plasma zinc is tightly bound to alpha 2-macroglobulins, and to other serum proteins. Transferrin can also bind zinc and might play a role in the distribution of zinc in the portal venous system.[7]

Biochemistry and Physiological Role

More than 20 different zinc metalloenzymes have been identified, the first one being carbonic anhydrase which was found in 1940 to contain 0.3 percent zinc. In mammalian tissues carboxypeptidase A and B, alkaline phosphatase, alcohol

TABLE 1.—*Zinc Concentrations in Human Tissues and Body Fluids**

Tissue or Fluids	Zinc Concentration (μg/gram wet weight)
Adrenal	6
Blood	7
Bone	66
Brain	13
Gastrointestinal tract	21
Hair	175
Heart	27
Kidney	37
Liver	38
Lymph nodes	14
Muscle	48
Ovary	12
Plasma	0.7
Prostate	87
Skin	6
Spleen	19
Sperm	125
Urine	0.3

*Values adopted from References 5 and 6.

dehydrogenase, retinene reductase and lactic-, glutamic- and d-glyceraldhyde-3-phosphate dehydrogenase are known zinc metalloenzymes. Superoxide dismutase contains two atoms of zinc and two atoms of copper. The latter enzyme, also known as erythrocuprein, protects cellular structures from damage by superoxide radicals, generated for example, in the oxidation of xanthine to uric acid by xanthine oxidase.

In addition to both the structural and catalytic functions that the metal exerts in these metalloenzymes, zinc plays an important role in nucleic acid metabolism and protein synthesis. In zinc-deficient animals, the *in vivo* incorporation of thymidine into DNA is decreased and the activities of thymidine kinase, and nuclear DNA-dependent RNA polymerase are reduced. Ribonuclease activity is inhibited by zinc, suggesting that an adequate zinc supply is necessary to prevent excessively rapid RNA degradation. Normal polysome formation is also diminished in the brains of zinc deficient rats.[8] These experimental findings show the essentiality of zinc in the processes of nucleic acid metabolism, protein synthesis and cell division.

Experimental zinc deficiency has been produced in many animal species and also occurs in field conditions. Since the zinc requirements of young growing animals are relatively large, the effects of nutritional deficiency are more striking. Many of the experimentally produced features have now been described in humans. Prominent findings include growth failure and anorexia. Food intake decreases and growth velocity diminishes quickly. The growth inhibition results partly from decreased food intake, but also from impaired utilization since attempts at forced feeding lead to worsening in the condition. The anorexia resolves rapidly after zinc supplementation of a deficient diet.

Hypogonadism with absent spermatogenesis and failure of development of primary and secondary sex organs in males and adverse effects on reproductive processes in females are regularly found in experimentally induced zinc deficiency. Even short-term zinc deficiency in pregnant rats results in a multitude of congenital malformations, particularly of the central nervous system and abnormalities in preimplantation embryos have been elicited by maternal zinc deficiency in the early stages of pregnancy.[9]

In zinc deficient animals epidermal changes are pronounced, with alopecia, dermatitis and disorders of keratinization. Skeletal changes include bowing of legs and stiff joints. Hypoplasia of lymph nodes and thymus has been observed, therefore indicating a requirement of zinc for normal development of immune functions. Impaired mobilization of hepatic vitamin A stores results in decreased serum levels in zinc deficient rats.

Metabolism

Absorption of zinc occurs mainly in the duodenum and the proximal small intestine. The mechanism probably involves an active transport, facilitated by low molecular weight ligands of pancreatic origin. The ligands bind zinc and transport it to the luminal surfaces of the intestinal epithelial cell. From there, zinc is transferred to a binding site on the basolateral membrane, where it becomes available for attachment to albumin and transferrin proteins in the portal circulation.[10] The percentage of dietary zinc absorbed varies from 20 percent to 80 percent with most reported values approximating 20 percent to 30 percent. Absorption depends partly on the existing nutritional status and partly on the level of intake. Preexisting deficiency enhances absorption, which is also affected by the physical and chemical properties of the diet. Zinc from animal sources is generally better absorbed than that from plant products. This is partly due to the phytate content of plants—phytate binding zinc in the intestinal lumen and rendering it unavailable. Fiber apparently exerts a similar effect. In

animals, an increase in the calcium content of the diet, in the presence of phytate, reduces the availability of zinc through formation of an insoluble calcium-zinc-phytate complex. Conversely, chelating agents, whether natural such as casein in milk or artificial (EDTA) can compete with phytate and increase availability.

Other metals may also interfere with absorption, copper and zinc being mutually antagonistic. Both metals possess a common path in absorption, when they attach to a sulfhydryl-rich protein in the cytosol of duodenal mucosal cells. This protein, one of the metallothioneins, has a molecular weight of approximately 10,000 daltons. Cadmium, which also attaches to metallothioneins, similarly interferes with zinc absorption in animals.

Studies with zinc 65 in humans show the presence of the isotope in plasma within 15 minutes of oral administration, peak levels being reached within two to four hours. The highest turnover and retention of radioactive zinc occur in the liver, kidneys and spleen. Most of the hepatic zinc is present in the cytosol, bound to hepatic metallothionein. Muscle and red blood cell uptake of the isotope is slower with bones, brain and hair showing even slower turnover rates. Twenty-one days after administration of the isotope 70 percent had been excreted in the feces, 2 percent in urine and 28 percent remained in the body.

The main route of excretion of zinc occurs in the intestine. Fecal zinc consists mainly of unabsorbed dietary zinc with a small contribution from intestinal cell shedding and zinc of biliary and pancreatic origin. Fecal losses of zinc in adults consuming 15 mg of dietary zinc, approximate 10 mg a day.

Urinary losses of zinc are between 0.3 and 0.5 mg per 24 hours, primarily as amino-acid bound zinc with some porphyrin-bound zinc. Glomerular filtration of amino-acid bound plasma zinc would result in excretion of approximately 2 mg per day, consequently a mechanism for tubular reabsorption of amino-acid bound zinc must exist.[5] The zinc concentration in sweat approaches 115 μg per dl and under conditions of extreme heat, losses of 2 to 3 mg per day may occur.

Nutritional Requirements

Zinc is considered to be an essential nutrient, which means that a minimal daily intake must be provided for maintenance of optimal health. There are no reserve stores of zinc, such as ferritin for iron, and the large quantities of zinc found in bone and muscle do not seem to be readily available for mobilization. The Food and Nutrition Board, National Research Council, National Academy of Sciences, added zinc to the list of Recommended Dietary Allowances in 1974.[11] The recommended daily intakes are 3 mg for infants, from birth through 4 months of age and 5 mg from 5 through 12 months. Toddlers and children—1 to 10 years old—should receive 10 mg daily. An intake of 15 mg of zinc is recommended for adolescent and adult males and females, but for the latter requirements increase to 20 and 25 mg, respectively, during pregnancy and lactation.

The availability of zinc in the diet varies with the nature of foods, with zinc from animal sources being generally more available for absorption than that from plant products. Shellfish contain high concentrations of zinc, meats and nuts are good sources and while grains and raw sugars contain adequate quantities of zinc, partitioning of the grains and refining of the sugars will remove most of the available zinc. Large variations in daily intakes, from 5 to 29 mg per day, have been reported for men.[12] Representative zinc concentrations of a variety of foods are shown in Table 2.

Zinc Deficiency in Humans

In the last 20 years there have appeared increasing numbers of reports of beneficial effects of zinc supplementation in a variety of disease states. These studies have shown the importance not only of an adequate nutritional intake of zinc, but also of the bioavailability of dietary zinc. The major effects of zinc deficiency in humans are changes in growth, sexual maturation and function, appetite, the senses of taste and smell, epithelial structures and processes such as wound healing. There is also growing interest in the roles that metals such as iron and zinc play in the processes of cognitive and psychological function and in the maintenance of normal immunocompetence. Historically, human zinc deficiency was first reported from Middle Eastern countries, and this discovery created impetus for further research.

Adolescent Dwarfism in Middle Eastern Countries

Prasad and collaborators in 1961 described a new syndrome of dwarfism with anemia, hepatosplenomegaly and hypogonadism, and they

postulated that zinc deficiency was the causative factor of the lack of growth and sexual maturation.[4] This report originated from Iran where nutritional dwarfism is found among approximately 3 percent of male inhabitants of rural villages. These adolescents and young men generally have the physical appearance of 10-year-old boys, with growth retardation and absent sexual development. They often have a rough skin and spoon nails, the bone age is delayed and the epiphyses of long bones remain open. Anemia and hepatosplenomegaly were concomitant findings and both were corrected with administration of iron. Most of the subjects in Iran were clay-eaters, some complained of lack of appetite and two of the original ten patients had night blindness. A serum zinc level was obtained in only one patient and was found to be low. A similar syndrome was found in Egypt, where, however, the anemia was not so profound and the hepatosplenomegaly less pronounced. Studies of zinc metabolism in Egyptian dwarfs showed decreased zinc levels in plasma, red blood cells and hair, a diminished exchangeable zinc pool, and decreased excretion of radioactive zinc in urine and feces, the latter finding being indicative of zinc conservation in a deficiency state.[15] The pathogenesis of the iron and zinc deficiency was investigated and three possible causes were envisaged. The diet of the Iranian and Egyptian dwarfs consisted mainly of unleavened wheat bread, which has a high phytate content. The latter can bind dietary iron and zinc and render them unavailable for intestinal absorption. In some patients, increased urinary blood losses from schistosomiasis with subsequent excretion of iron and zinc was considered to be another cause. Third, in hot climates excessive sweating could also enhance zinc losses and lead to a deficiency state. There followed considerable controversy on the role that zinc-deficiency had in this syndrome, until, in 1972, Halsted and collaborators published the results of a controlled study of zinc supplementation in 14 such dwarfs.[16] The subjects who received zinc supplements, in addition to a well-balanced diet, showed greater growth velocities and earlier onset of sexual maturation than the controls who received the well-balanced diet alone. The unleavened breads eaten by the Iranian villagers, whose diet contained little animal protein, were further found to contain 40 percent more phytate than the leavened breads consumed by urban inhabitants, presumably because fermentation destroys phytate.

TABLE 2.—*Examples of Zinc Content of Individual Food Items**

Foods	*Zinc Content: mg/100 grams*
Beef: round steak	5.0-6.00
Liver	3.80
Chicken	
leg	2.80
breast	0.90
Oysters	
Atlantic	74.70
Pacific	9.00
Whitefish	1.00
Tuna: canned	1.00
Peanuts and peanut butter	2.90
Wheat: whole grain	3.40
Bread	
whole wheat	1.80
white	0.60
Rice: polished	0.4-0.70
Lima beans	
raw	2.80
cooked	1.00
Peas	0.70
Potato chips	0.81
Carrots	0.40
Butter	0.10
Milk	0.35
Corn oil margarine	0.20
Cheese: domestic mozarella	3.88
Orange juice	0.07

*Data from References 12, 13 and 14.

Wound Healing

If one considers that wound healing is a process in which active cell growth and protein synthesis are occurring, it is not surprising that a deficiency of a nutrient essential for normal growth would result in impaired wound healing.[17] Animal studies showed that zinc supplementation accelerated the rate of healing of surgical wounds, mainly through enhancement of the rate of epitheliazation. Conversely, zinc-deficient animals show striking changes in epidermal and epithelial structures. In humans, zinc supplementation has allowed healing of chronic leg ulcers and indolent wounds which were previously refractory to treatment.[17] While some contradictory results were obtained in studies on the effects of zinc in healing, there is now general agreement, that zinc supplementation will improve the rate of healing in patients with laboratory evidence of inadequate zinc nutriture. Clinical experience shows that patients with malnutrition, malignant conditions, pulmonary infections and atherosclerosis heal poorly. Massive urinary losses of zinc occur after major burns, and zinc deficiency occurs frequently in

patients in hospital as a result of poor nutritional intake previously and of derangements in zinc homeostatic metabolic functions with increased urinary and fecal losses. In the presence of delayed healing, laboratory evaluation of zinc status should be accomplished and supplementation considered. This subject is covered in an excellent review by Pories and co-workers[18] who recommend 220 mg of zinc sulfate heptahydrate (45 mg Zn^{++}) three times per day. These quantities of zinc correct hypozincemia and enhance wound closure in zinc-deficient subjects. Pories has also reported that zinc supplementation decreased the time required for healing of pilonidal cyst surgical wounds in young adults. Also of interest is a report from Australia where zinc supplementation improved the frequency and rates of healing of gastric ulcers.[19]

Zinc and the Senses of Taste and Smell

Many diseases are accompanied by decreased taste (hypogeusia) and smell acuities (hyposmia) and distortions of taste (dysgeusia) and smell (dysosmia) can also occur. While these complaints are often of short duration—during upper respiratory infections, acute hepatitis or the first trimester of pregnancy—they sometimes persist, and may be most inconvenient and lead to weight loss.[20] Hypogeusia can occur during copper depletion with D-penicillamine and can be corrected by the administration of exogenous copper or zinc. These observations led to the empirical administration of zinc sulfate to patients with disorders of taste and smell and the results of the initial placebo-controlled study seemed encouraging. However, in a later double-blind study both zinc sulfate and placebo were found to exert equivalent effects.[21] Anorexia and hypogeusia appear rapidly, though, when zinc depletion is experimentally produced, through administration of l-histidine for example, a microligand that enhances urinary zinc losses.

The importance of zinc in the maintenance of taste acuity and of a normal appetite was also shown in children by Hambidge and associates.[22] These authors carried out a survey of trace element concentrations in hair and they found that ten of a group of 132 apparently normal children, aged 4 to 16 years, had hair zinc levels less than 70 μg per gram, more than 3 SD below the adult mean and in the range of hair zinc levels of Middle Eastern dwarfs. When additional information was obtained, eight of the ten children were noted to be below the 10th percentile for height, with the poor growth not explainable on a familial basis. These children were described as poor eaters, with a particular distaste for meats, and objective hypogeusia was shown in five of the six children in whom taste acuity was measured. Supplementation with small doses of zinc (0.2 to 0.4 mg per kg of body weight per day) was followed by correction of the taste acuity defects within one to three months. The authors concluded that these apparently normal children were suffering from a dietary deficiency of zinc, sufficient to impair taste acuity and possibly also sufficient to decrease appetite and limit growth velocity.

Zinc and Growth of Infants and Children

In the same survey of hair zinc concentrations, Hambidge and co-workers found that infants and young children had hair zinc levels much lower than at birth, where hair zinc levels equaled adult levels. The plasma zinc levels of infants in Denver were also found to be lower than mean adult levels, a finding which differed with reports from other countries.[23] These observations prompted a search for explanations, one of which was the relatively low zinc content of some American infant milk formulas. In the fabrication of these formulas skimmed cow's milk is diluted to reduce the protein content to levels closer to those of human breast milk. This dilution is accompanied by a concomitant reduction in zinc content, to a final concentration of 1.8 mg per liter, whereas most whole milks contain 3 to 4 mg per liter.

There followed a study on the effects of supplementing Similac with 4 mg of elemental zinc per liter. This study was done in a double-blind controlled manner with anthropometric measurements and determinations of plasma zinc levels at determined intervals.[24] One surprising observation was that male infants receiving the zinc-supplemented product had significantly larger increments in length and weight gains than the control infants, receiving the nonsupplemented formulas. The test and control female infants did not show any differences in growth rates. The results suggested that zinc requirements of growing male infants may be higher than for females, a finding previously noted in two animal species, and that the zinc content of the formulas, before 1975, when supplementation was started, was

insufficient to ensure optimal growth of male infants.

Marginal zinc deficiency in children had been found in Iran, where a controlled trial of zinc supplementation resulted in significant differences in height and weight gains and in bone age maturation, together with a tendency towards accelerated maturation of sexual development.[25] Marginal zinc deficiency, however, was not suspected in this country until recently, when Sandstead[3] calculated that infants, pregnant women, teenage and college women, and elderly persons in institutions were living on diets of marginal or deficient zinc content. Support for this hypothesis is coming from nutritional studies of varied American population groups including vegetarians,[26] elderly persons,[27] and preschool children from low-income families.[28] Decreased mean levels of zinc in plasma and hair were found in a group of Denver preschool children who were selected, upon entry to Head Start schools, because of low growth percentiles. Whether zinc-supplementation will improve growth velocities in such children subsisting on low-income budgets remains yet to be determined.

Acrodermatitis Enteropathica

Acrodermatitis enteropathica is a rare disease, of autosomal recessive inheritance, the onset of which occurs during infancy. Gastrointestinal dysfunction with diarrhea and vomiting, extensive acral and periorificial skin lesions of eczematous or vesicular-bullous type, and alopecia are the principal clinical findings. Growth retardation, paronychia with nail dystrophy, ocular symptoms of blepharitis, conjunctivitis and corneal opacities, stomatitis, cheilitis and emotional lability also occur frequently. The time of onset depends on the presence and duration of breast-feeding, clinical manifestations generally appearing one or two weeks after weaning. If susceptible infants are not breast-fed the symptoms will develop in the first four to ten weeks of life. Secondary intercurrent infections with bacteria and yeast, combined with progressive malnutrition often resulted in death within one to three years of life. In 1953 the usefulness of 8-hydroxyquinoline derivatives was shown for the control of symptoms; the mechanisms were unknown but now are thought to be related to the chelating properties of these compounds, which enhance intestinal zinc absorption.[29] In 1973 Moynahan recognized the similarity between the findings in acrodermatitis enteropathica with those of experimentally induced zinc deficiency in animals.[1] This observation occurred during the course of treatment of a child with lactase deficiency in addition to acrodermatitis enteropathica, who was maintained on a synthetic diet and on hydroxyquinoline treatment. Relapse of symptoms led to an analysis of the diet which was found to contain very little zinc. Administration of the metal was accompanied by disappearance of lesions, which recurred when the zinc supplement was inadvertently withheld by the patient's mother. Subsequent studies (for a recent review see reference 29) confirmed the presence of a severe zinc deficiency state in this disease, presumably caused by a defect in intestinal absorption of the metal. The defect can fortunately be overcome by the daily administration of 1 to 2 mg of zinc per kg of body weight. This results in bringing to normal levels the laboratory indicators of zinc nutrition and is accompanied by catch-up growth spurts in prepubertal children.[30] Prolonged administration of human milk was another therapeutic modality which was used in patients with this disease who could not tolerate hydroxyquinoline derivatives. Studies by Dr. Hurley's group[31] have shown that zinc in breast milk is bound to a low molecular weight protein which seems to enhance intestinal zinc absorption, therefore providing an explanation for the therapeutic effect of breast milk. There has been a recent report on a variant of acrodermatitis enteropathica without hypozincemia in which abnormally high concentrations of zinc were found in serum, epidermis and dermis.[32] This variant may represent another disorder of zinc metabolism, where intracellular zinc is chemically bound and unavailable for biologic activity.

Hereditary Hyperzincemia

Another inherited disorder of zinc metabolism was described in 1976 when Smith and collaborators[33] studied the family of a 28-year-old black man in whom levels of zinc in plasma were found to be extremely high (greater than 300 μg per dl). Elevated plasma zinc levels were found in four of the patient's siblings, in his son and in one of his two nieces. Fractionation of serum proteins showed that most of the excess zinc was bound to albumin, and the results of a test zinc load showed that the binding capacity of the serum proteins was not saturated. The zinc levels of hair, nails and erythrocytes were normal in this subject. While hyperzincemia is a rare find-

ing, it should no longer be dismissed as simple contamination of a blood sample.

Acute Zinc Deficiency With Total Parenteral Nutrition

Kay and Tasman-Jones in 1975 described a syndrome which resembled acrodermatitis enteropathica and occurred during intravenous hyperalimentation with solutions containing only trace amounts of zinc.[34] The clinical findings were periorificial dermatitis, diarrhea, alopecia and pronounced depression. Massive hyperzincuria, up to 25 mg per day was noted in one of the patients following a period of prolonged catabolism complicated by sepsis. The hyperzincuria decreased when the patients were gaining weight, but at that time the plasma zinc levels fell and the clinical symptoms appeared. Later studies have shown increased urinary zinc excretion during parenteral nutrition, presumably caused by an excess amount of amino acid bound zinc being presented for tubular reabsorption.[35] In patients receiving parenteral alimentation, the development of periorificial rashes, depression, alopecia or diarrhea indicates the necessity of laboratory evaluation of zinc metabolism. The response to zinc supplements is rapid with mood improving first and skin changes thereafter.

Zinc and Immunocompetence

Impaired cellular immunity has been noted in zinc deficient animals and similar findings are being reported in humans. Pekarek and co-workers showed there to be impaired delayed skin reactivity to dinitrochlorobenzene and depressed lymphocyte transformation capacity in a 17-year-old boy with acquired zinc deficiency.[36] A normal lymphocyte response and delayed skin reaction were obtained three weeks after zinc therapy. Supplementation in eight children who had recovered from protein-energy malnutrition with 2 mg of zinc per kg of body weight per day was accompanied by significant increases in thymic size, as judged by chest radiological examinations.[37] In an extension of their previous studies, Golden and associates measured delayed-hypersensitivity reactions in ten children with protein-energy malnutrition using skin tests with Candida antigen.[38] Each child served as his own control, one arm being covered with a placebo ointment, the other with 1 percent zinc sulfate in the same emulsifying ointment. It is known that zinc can be absorbed transcutaneously from zinc sulfate ointments and the delayed hypersensitivity responses were larger at the zinc treated injection sites. The degree of enhancement of the response correlated negatively with the plasma zinc concentration at the time of testing. These studies indicate that zinc deficiency depresses T-cell response and, therefore, may be a factor in the increased susceptibility to infections in conditions such as protein-energy malnutrition. Impaired monocyte and neutrophil chemotaxis has also been shown in acrodermatitis enteropathica, with correction of the defects with zinc treatment.[38]

Sexual Function in Renal Failure

Antoniou and her colleagues carried out an elegant controlled study on eight impotent men being treated for renal failure by hemodialysis.[40] Four of the impotent subjects received zinc supplements orally for six months, but there was only a slight increase in the previously low plasma zinc levels. Zinc chloride was then added to the dialysis solution in amounts sufficient to maintain the plasma zinc levels between 100 and 150 mg per dl. Within two to four weeks there was a striking improvement in potency in the four patients, which was accompanied by an increase in testosterone and follicle stimulating hormone values in plasma to normal levels. No changes were noted in the four patients receiving placebos. This observation confirms the importance of zinc for normal function of the pituitary-testicular hormonal axis and suggests that zinc deficiency may be a reversible cause of sexual dysfunction in subjects with renal failure. The causes of zinc deficiency in such subjects still remain unclear.

In another study of male subjects with oligospermia, zinc supplementation was accompanied by increased levels of plasma testosterone and increase in sperm count.[41] These impressive findings should provide impetus for further research on zinc metabolism in patients with reproductive dysfunctions.

Zinc and Chronic Liver Disease

Zinc and chronic liver disease is a complex subject which has been recently reviewed by Sullivan and Burch.[42] For more than 20 years it has been known that patients with cirrhosis had decreased levels of zinc in plasma and increased urinary excretion of zinc. The reasons for the latter are not well understood but may relate to changes in the quantities of amino acid bound zinc circulating in the plasma compartment. In

TABLE 3.—*Etiological Factors in Zinc Deficiency*

Factors	*Examples*
Inadequate dietary intake ...	Low-income diets Old age Protein-calorie malnutrition
Increased zinc requirements .	Rapid growth Pregnancy Lactation Tissue anabolism
Decreased availability	Phytate Fiber
Decreased absorption	Malabsorption syndromes Steatorrhea
Excessive losses	Hyperzincuria Surgery Burns Increased sweating Blood losses
Iatrogenic	Chelating drugs (penicillamine) Parenteral nutrition
Genetic defects	Acrodermatitis enteropathica

alcoholic persons the dietary zinc intake would be expected to be marginal, which, with increased excretion, would facilitate the development of a zinc deficiency state. Zinc is a component of alcohol dehydrogenase which, in the liver, catalyzes the first step of alcohol metabolism, and in the retina regenerates retinal aldehyde from retinol. The latter mechanism is necessary for adaptation to darkness. Abnormalities of dark adaptation are frequently found in alcoholics with cirrhosis and respond to both supplementation with zinc[43] and with vitamin A.[44] Interactions between zinc and vitamin A metabolism have been shown in rats, in which the mobilization of hepatic stores of vitamin A is a zinc-dependent process.[45] By facilitating the synthesis of retinol-binding protein, one of the vitamin A plasma transport carriers, zinc may be exerting its beneficial effect in reversing night blindness, although a direct effect on retinal alcohol dehydrogenase is not to be excluded.

Another relation between zinc and liver disease that deserves further study derives from the observation that ornithine transcarbamylase activity is decreased in zinc deficient animals. Elevations of blood ammonia and decreased levels of blood urea nitrogen are also found in cirrhotic patients. Consequently, in the treatment of alcoholic patients zinc supplementation should certainly be considered in addition to correction of other nutritional deficiencies.

Other Conditions Associated With Zinc Deficiency

Zinc deficiency states can develop in many circumstances and some of the etiological contributory factors are summarized in Table 3. Retarded growth with delayed puberty can occur in sickle-cell disease patients, where excessive urinary zinc losses result from increased red blood cell destruction.[46] Similarly, the adolescent dwarfism syndrome has been described in patients with intestinal malabsorption[3] and most recently with cystic fibrosis.[47] In rheumatoid patients encouraging results were found with zinc sulfate supplementation. Low serum zinc levels had previously been noted in rheumatoid arthritis by other investigators and the study with zinc supplementation was based on the premise that zinc is necessary for normal synovial function and also to facilitate host-resistance to the disease process.[48]

Skin Diseases and Zinc

Michaelson[49] started using zinc supplements in patients with acne after noting that in one of his patients with acrodermatitis enteropathica there was a pronounced decrease in acne lesions after onset of treatment with zinc. Two controlled studies have thereafter shown that orally given zinc sulphate was a useful therapeutic agent in the treatment of acne. In one of the studies both zinc and tetracycline caused a 70 percent decrease in acne scores.[49,50] Scribner has also recommended zinc supplements in low doses for persons with socially unacceptable perspiration odor.[51]

Diagnosis of Zinc Deficiency States

The diagnosis of zinc deficiency is not an easy one. Zinc levels in plasma are decreased in many acute situations. In an elegant study, Falchuk showed that the decrease in zinc levels in plasma was caused mainly by a decrease in albumin-bound zinc, an effect that could be reproduced by adrenocorticotropic hormone (ACTH) infusions.[52] Whether the decreases in plasma zinc caused by leukocyte proteins and endotoxins[53] is mediated through ACTH remains yet to be determined. Persistence of decreased levels of zinc in plasma after an acute illness probably represents a good indicator of a deficiency state. Determination of hair and erythrocyte levels of zinc may be useful in conditions in which zinc deficiency has been of long duration. The measurement of urinary zinc excretion may be helpful. If the urinary zinc values are high in the presence of decreased plasma

levels, this would indicate disturbances of zinc metabolism. If the urinary levels of zinc are low, it may be indicative of body conservation.

In the presence of poor growth, decreased appetite, lack of smell, poor wound healing, impaired sexual maturation or function, zinc deficiency should be considered. Diminished night vision in alcoholics and depressed mood in elderly persons may be indicators of marginal deficiency. Perhaps measurement of delayed skin sensitivity with topical application of zinc sulphate ointment may be useful to detect borderline deficiency states. The response to zinc supplements will often provide an answer as to whether the patient was in some degree zinc deficient.

Treatment of Zinc Deficiency States

Zinc is well absorbed as the oxide, carbonate, sulfate or metal. The sulfate is generally used at doses of 5 to 10 mg per kg of body weight per day, which provide 1 to 2 mg of zinc per kg of body weight per day. Lesser doses may sometimes be used. In surgical patients receiving 220 mg of zinc sulfate three times a day, 5 percent reported gastrointestinal upsets that ceased when treatment was stopped. No side effects have been reported with doses of 1 mg of zinc per kg of body weight per day. Administration of zinc supplements with meals decreases the incidence of gastrointestinal symptoms, but may adversely affect zinc absorption.

Intravenous requirements for patients receiving parenteral alimentation remain yet to be determined exactly. They approximate 30 to 40 μg per kg of body weight per day. Intravenous dosage for correction of deficiency states has not really been determined, either, and many patients can tolerate oral administration of zinc supplementation even in short bowel syndromes.

Toxicity

Zinc is relatively nontoxic and a good margin exists between physiologic requirements and toxic doses. Zinc toxicity with diarrhea and vomiting has occurred in persons drinking lemonade mixed in galvanized cans. Zinc fever has been described accompanied by profound anemia in a patient receiving hemodialysis with zinc contaminated water. Acute intravenous zinc poisoning resulting in death occurred after the inadvertent administration of 7.4 grams of zinc sulfate intravenously.[54] However, ingestion of 12 grams of metallic zinc by a 16-year-old boy resulted only in pronounced lethargy.[55]

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Glomerular Filtration Rate as a Useful Measurement in Patients With Sepsis

I THINK one of the most useful measurements you can make in a patient with sepsis or any other patient is the glomerular filtration rate (GFR)—just a one-hour creatine and clearance determination. Any laboratory will do it; it is simple to do. Once you have gotten the GFR up to normal, because of the phenomenon of autoregulation you cannot drive it any higher no matter how much fluid you give. And it is the GFR that determines how much nitrogen is going to be excreted. So I think the answer is that when you have given enough fluid, so that the GFR is up to a relatively normal value for that patient, further fluid cannot possibly be of any value in clearing nitrogenous wastes.

—SAMUEL R. POWERS, JR., MD, *Albany, New York*
Extracted from *Audio-Digest Surgery* Vol. 24, No. 19, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206

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Nutrition for Physicians:

A Selected Bibliography

MARION NESTLE, PhD, *San Francisco*

THE PERFECT NUTRITION HANDBOOK for physicians has yet to be written. Such a book would encompass basic principles of nutrition and assessment of nutritional status, pathophysiology of diseases of dietary deficiency or excess, and the specific methods, based securely on available research evidence, for prevention and treatment of these illnesses. Because the evidence that links diet to disease is often inconclusive, critical evaluation of research results becomes the key issue in nutrition applied to medical practice.

Among the deluge of nutrition books published within the last few years, the ones listed here are distinguished by an unusually responsible attempt to present what is actually known about one or another aspect of this field. Each of these volumes includes an excellent reference list; the books especially suited for recommendation to patients are marked with an asterisk.

Human Nutrition and Dietetics, Sixth Edition—S. Davidson, R. Passmore, J. F. Brock, and A. S. Truswell. Churchill Livingstone, 1975 (seventh edition due fall 1979).

This comprehensive introduction to clinical nutrition comes closest to the ideal handbook for physicians; it only lacks details on treatment. The book provides concise summaries of nutrition history and body composition, and basic nutrition facts and concepts. Separate chapters discuss each of the important nutritional diseases and an entire section is devoted to public health. Most of the Anglo-Scottish text translates well to American medicine; the occasional references to porridge, haggis and kilojoules seem a small price to pay for this otherwise helpful book.

Modern Nutrition in Health and Disease, Fifth Edition—R. S. Goodhart and M. E. Shils (Eds). Lea and Febiger, 1973 (sixth edition to be published October 1979).

This huge (1,153 pages) compendium of review articles is the classic United States textbook of clinical nutrition. Its size is at once its great strength and weakness. The information content is vast; each chapter is based on an exhaustive literature review (for example, "Nutrition in Pregnancy": 206 references) and readers must struggle to select needed facts from among the mass of detail.

Nutrition Reviews' Present Knowledge in Nutrition, Fourth Edition—The Nutrition Foundation, 1976.

More than 50 brief articles by as many authors make this book a handy and inexpensive ($8.50) place to discover quickly the latest research results in selected areas of basic and applied nutrition.

Nutritional Support of Medical Practice—H. A. Schneider, C. E. Anderson, and D. B. Coursin (Eds). Harper and Row, 1977.

Many (45) authors produced 32 review articles on nutrition applied to each of the medical specialties. The book's orientation is decidedly clinical; basic concepts are handled in four short chapters. The major focus is on utilization of nutrition to improve the outcome of medical and surgical treatment of disease. Although the chapters are of uneven quality and are occasionally repetitious, the book is a useful introduction to clinical nutrition.

Manual of Surgical Nutrition—Committee on Pre and Postoperative Care, American College of Surgeons. Saunders, 1975

The special interests of surgeons are emphasized in this collection of 22 reviews of fundamental metabolic concepts and the role of nutrition in caring for catabolic surgical patients. Discussions of wound healing, infections, body temperature regulation, enteral and parenteral feeding, and specific disease conditions requiring surgical intervention range from the absolutely basic (amino acid structures) to sophisticated detailed instructions for inserting indwelling central venous feeding catheters. The text is not light reading, but it provides a survey of the important nutrition issues that confront surgical practice.

Dr. Nestle is Associate Dean, School of Medicine, and Lecturer in Biochemistry and Biophysics, University of California, San Francisco.

Infant Nutrition, Second Edition—S. J. Foman. Saunders, 1974.

Although this book focuses on nutrition in pediatric practice, it includes so sound a discussion of fundamentals that it qualifies easily as a general introduction to clinical nutrition. Dr. Foman's clinical perspective relies strongly on the results of his own and others' research; his judgments are consistently persuasive, and he is one of the very few writers on nutrition who frankly labels speculation as such.

The Obese Patient—G. A. Bray. Major Problems in Internal Medicine Series, Volume IX. Saunders, 1976.

Everything the physician needs to know about the definition, course, risk and treatment of obesity is presented with refreshing clarity and absolute authority in less than 500 pages.

Drug-Induced Nutritional Deficiences—D. A. Roe, Avi, 1976.

This monograph presents compelling evidence for the importance of drugs in the cause of malnutrition. Separate chapters review each of the major drug groups that affect appetite, or the absorption, utilization or excretion of nutrients. A major concern of the author is the effect of chronic drug usage on the already compromised nutritional status of geriatric patients.

***Nutrition, Weight Control, and Exercise**—F. I. Katch and W. D. McArdle. Houghton Mifflin, 1977 (in paper, $8.95).

This is *the* book to recommend to patients who run or who want to. Fundamentals of nutrition are well illustrated and made relevant through continual reference to physical fitness and health. The sections on energetics, aerobics and diet manage to simplify essential concepts without losing accuracy. The do-it-yourself calorie tables entertain: one Quarter Pounder is 557 Kcal; a 150-pound cellist must play 3.3 hours to work it off.

***Laurel's Kitchen**—L. Robertson, C. Flinders, and B. Godfrey. Nilgeri Press, 1976 (Bantam paper edition, 1978).

The last 150 pages of this handsome vegetarian cookbook make up the most intelligent and best written popular introduction to nutrition to be found in local bookstores. This section, titled "Nutrition for a Meatless Diet," summarizes basic principles of nutrition in an easily accessible manner; omnivores will also learn from it. Lists of foods containing each required nutrient and well-organized food composition tables are included, all meat-free. The recipes are wonderful and directions may be accompanied by comments on food composition or caloric content. Recommend this book to everyone but warn career women to ignore the introduction; it extols the virtues of home, kitchen and housework.

***Diet for a Small Planet, Revised Edition**—F. M. Lappé. Ballantine, 1975.

Why are the good, interesting nutrition books written by vegetarians? This one stresses amino acid complementarity in the preparation of vegetarian foods. Lappé takes a serious look at the way meat is produced in this country, and presents a compelling argument for eating low on the food chain. The recipes calculate required amounts of well-balanced protein for each meal.

***Dietary Goals for the U.S., Second Edition**—U.S. Senate Select Committee on Nutrition and Human Needs, 1977 (U.S. Gov't. Print. Office Stock No. 052-070-04376-8).

This is the complete text of the controversial McGovern Committee report on the relationship between diet and killer diseases that recommends sweeping changes in the typical diet in the United States—eat more complex carbohydrates (fruits, vegetables, whole grains); eat less fat (meat, dairy products), sugar and salt. The evidence for these conclusions is presented; it is incomplete, but the report urges immediate dietary action.

***The Changing American Diet**—L. Brewster and M. Jacobson. Center for Science in the Public Interest, Washington, DC, 1978 (and only $2.50).

The United States Department of Agriculture's fascinating statistics on American food consumption patterns since 1910 are presented in simple graphs accompanied by an informative text. Here are the data to fuel your own speculations on the dietary changes that might be responsible for heart disease and the other major ailments of this affluent society.

***Guide to American Food Programs**—A Report of the Food Law Center. California Rural Legal Assistance, 1977 (single copies available free from the Center at 115 Sansome St., San Francisco, CA 94104).

This pamphlet summarizes the history, legal status, eligibility requirements and benefits of the important United States food supplementation programs along with simple instructions and worksheets for determining income eligibility. Low-income patients will appreciate this resource.

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The Challenge of Nutritional Maintenance in Cancer Patients

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Weight loss and cachexia frequently accompany malignant disease and its treatment. Semistarvation is common in patients in hospital and in patients with cancer as well. Adequate nutrition is essential in treatment of malignant conditions. Patients and families as well as the medical community should use a comprehensive approach to improving the caloric and protein intake of patients who are still able to benefit from oral intake and further therapy.

MANY VOLUMES of published data affirm the benefits of good nutrition in cancer patients. Often there are multiple causes of malnutrition, usually related to the cancer itself or to systemic effects of the cancer. Treatment with chemotherapy, irradiation and surgery, as well as psychological difficulties, are also aggravating factors.

Physicians must be attuned to the nutritional problems of patients for several reasons. First, they can foster in patients an awareness of the importance of adequate protein and calorie intake. In addition, physicians can reinforce the idea that adequate nutrition is an integral part of anticancer therapy without which other treatment modalities are less likely to succeed. They can stress that it is the responsibility of the patients and their families to carry out this aspect of their care.

Recent attention has centered on the use of hyperalimentation, or total parenteral nutrition (TPN), and elemental (chemically defined) diets in maintaining nutritional balance.

The important role of nutrition in cancer management is evident in the increased ability of patients to complete radiation therapy and chemotherapy, to suffer fewer complications during treatment and to achieve better surgical healing. This work has been done primarily with TPN and elemental diets.

It is hoped that similar benefits can be obtained with oral diets if attention to calorie and protein balance is maintained from the very beginning and malnutrition-induced changes in gastrointestinal function are thus prevented.[1] Otherwise anorexia, nausea, vomiting and bloating gradually develop when absorptive function of the gastrointestinal tract diminishes as malnutrition progresses, a process very difficult to reverse. Efforts must be made to prevent these changes caused by malnutrition.

This is, however, a difficult task to accomplish. The importance of nutrition must be discussed frankly with patients, with a reminder that it is their effort that will make the difference. While it is primarily the responsibility of the patient,

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family and friends to maintain an adequate diet for the former, the medical profession must also increase its efforts to help patients achieve a nutritious dietary program. Physicians can do this by discussing diet with patients, by providing written dietary instructions, by consulting with dietitians skilled in helping patients and physicians to solve nutritional difficulties, and by providing tape-recorded or video-taped discussions on nutrition. Doctors are responsible for educating patients in nutritional maintenance.

Parenteral Nutrition

Much current information concerning the effect of nutritional maintenance on anticancer therapy and its complications come from studies in parenteral nutrition. Several excellent reviews detail the method and results of hyperalimentation in cancer patients and others.[2-4] While these methods have contributed substantially to the ability to maintain nutrition and prevent starvation in cancer patients, as well as enabling the use of greater amounts of chemotherapy or fewer interruptions of radiation therapy, they will be mentioned only briefly in this discussion of oral nutritional maintenance. Basically, oral nutrition and parenteral nutrition work toward the same goal. The maintenance of adequate caloric and nitrogen status by either method should achieve the same result provided that the amounts of calories, amino acids, fats, carbohydrates, vitamins and minerals are adequate and that significant diarrhea, steatorrhea or malabsorption is not present.

Copeland treated 175 patients with TPN and recorded an average 2.5-kg (5.6-pound) weight gain during chemotherapy, a time when many patients lose weight.[5] There was a correlation between adequate nutritional status and response to chemotherapy. Those without TPN received 3.8 grams total dose of 5-fluorouracil and 10 percent responded, compared with 7.4 grams total dose and a 31 percent response rate in patients treated with TPN. With nutritional support as an adjunct to surgery, a group of 100 patients gained an average of 1.8 kg (4.2 pounds) in a period of 24.2 days. Weight gain, increase in strength and return of immunocompetence were much easier to accomplish when TPN was given preoperatively instead of postoperatively. This result underscores the need to prevent incipient starvation and its related systemic effects.

Heatley and Hughes, in England, reported that a group of patients who were treated with TPN for ten days before surgery for upper gastrointestinal malignancies experienced minimal postoperative morbidity and mortality, fewer wound infections and dehiscences, less postoperative pneumonia and shorter hospital stays.[6]

A group of 39 nutritionally depleted patients with a variety of malignancies received radiation therapy and TPN, and 95 percent of these patients were able to complete the planned radiation therapy.[7] There was a positive correlation between tumor response and nutritional status. It is critically important therefore to maintain protein and calorie intake from the beginning of treatment.

Nutrition also plays an essential role in the maintenance of immunological function.[8] Of 17 cancer patients who initially had negative results of skin tests of delayed hypersensitivity, 13 converted to positive test results after an average of 11.4 days of TPN, and only the converters responded to chemotherapy; those for whom results of skin tests remained negative (4 of 17) did not respond to chemotherapy.[9] After surgical operations, patients who had positive results of skin tests experienced uncomplicated postoperative recoveries. Since malnutrition does play a part in immune incompetence, immunologic dysfunction in cancer patients could be corrected if its cause is malnutrition.

One critical factor in the implementation of more intensive forms of alimentation is the potential for palliation or cure available through specific tumor-related therapy, be it chemotherapy, radiation therapy or surgery. Attempts at heroic measures of nutritional repletion seem unreasonable in patients whose tumors are not responsive to available agents. While vigorous refeeding seemingly might stimulate tumor growth,[10] this effect has *not* been seen by most researchers who have observed patients who received intensive nutritional supplementation.[5] Speculatively, however, although growth of a tumor during refeeding might theoretically seem detrimental to a patient, refeeding might stimulate more cells of a therapy-sensitive tumor to divide actively and enter the cell cycle, thereby decreasing the number of cells in the G_0, or resting, stage and increasing cell susceptibility to drug kill.[11]

Elemental Diets

Elemental diets that contain amino acids and other easily absorbable nutrients also have a place in nutritional therapy. They are commercially available under the names of Vivonex, Vivonex

HN, Flexical (all registered trade names) and others (Tables 1 and 2). These diets can provide 1,500 or more calories daily, and they have high nutritional value. Discussions of elemental diets are found in papers by Russell[12] and by Freeman and co-workers.[13]

In patients with advanced metastatic cancer, elemental diets decreased the number of rectal lesions induced by 5-fluorouracil treatment in human beings and helped patients maintain their weight.[14]

Bounous and associates found that, in rats, drug toxicity was decreased by the use of elemental diets before and after the administration of 5-fluorouracil.[15] These researchers felt that the diet helped to protect mucosal integrity, thus shielding animals from 5-fluorouracil-induced dipeptidase deficiencies. Elemental diets also significantly improved survival in mice following irradiation by enabling a faster recovery from radiation-induced intestinal lesions and by limiting the initial effects on absorptive cells.[16]

Diet Methods for Cancer Patients

Discussions of standard diets may be found in the *Mayo Clinic Diet Manual,*[17] in Iowa State University's *Recent Advances in Therapeutic Diets,*[18] in Goodhart and Shils' *Modern Nutrition in Health and Disease*[19] and in the *Diet Manual* from Massachusetts General Hospital's dietary department.[20] Some additions and changes in these diets are necessary for the special problems of cancer patients, which include complications from cancer therapy.

Radiation Therapy Problems

Radiation therapy to the head and neck area results in loss of taste, dry mouth, stomatitis and consequent anorexia. Irradiation destroys taste buds and decreases saliva secretion. It is extremely difficult to prepare food that will appeal to people who have undergone such treatment. The graphic description of the difficulties encountered after radiation therapy to the head and neck area written by MacCarthy-Leventhal should be read by all who treat patients with these tumors.[21] To stimulate appetite, food aromas and visually enticing foods must be substituted for foods that formerly tasted good. Patients who have undergone radiation therapy often need continual encouragement to eat, even though they are not hungry and find that swallowing is painful.

Foods such as citrus juices that may irritate sore mouths should be avoided. Patients are most comfortable with food taken at room temperature or slightly chilled. Highly seasoned foods may be irritating to the mouth and throat and do nothing to heighten taste that has been destroyed by therapy. Food sticking may be a problem, and swallowing can be difficult because of decreased saliva secretion. Meats and vegetables should be moistened with gravies and sauces to permit easier swallowing. A pureed diet may be tolerated better than a soft diet, depending on the degree of dysphagia present. Small frequent feedings are generally better accepted than are the customary three meals each day. High-protein, high-calorie, liquid supplements such as milk shakes, eggnog, Meritene, Sustagen and Carnation Instant Break-

TABLE 1.—*Overview of Nutritional Supplements*

*Supplement**	*Milk Base*	*Lactose-Free*	*Chemically Defined (Elemental)*	*Low Residue*	*Special Supplements*
Meritene	X	..	..	..	..
Sustacal	X	..	..	..	..
Sustagen	X	..	..	..	..
Nutri-1000	X	..	..	..	..
Carnation Instant Breakfast	X	..	..	..	..
Ensure	..	X	..	..	..
Flexical	..	X	X	X	..
Precision LR and Precision HN	..	X	..	X	..
Vivonex and Vivonex HN	..	X	X	X	..
Citrotein	..	X	..	X	X
Portagen	..	X	..	X	X
MCT	..	X	..	..	X

*All registered trade names.

TABLE 2.—*Oral Dietary Supplements (Commercially Available)*

Supplement‡ and Manufacturer	Ingredients	Form	Normal Dilution	Nutritional Analysis per Liter				Indication	Comments	Approximate Cost*	
				Kilo-calories	Protein (Grams)	Fat (Grams)	Carbo-hydrates (Grams)			Per Container	Per Ounce†
Meritene (Doyle)	Concentrated sweet skim milk, corn syrup solids, vegetable oil, sodium caseinate	Liquid	Not required	1,000	60.0	33.0	115	Supplemental nourishment	Various flavors available; milk base formula; high osmolarity may cause cramping or diarrhea.	10-oz can $.90	$0.09
	Specially processed, nonfat dry milk, corn syrup, maltodextrin	Powder	4 tbsp powder with 240 cc whole milk	1,000	69.0 (with whole milk)	35.0	119	Supplemental nourishment	Various flavors available; usually reconstituted with milk; high osmolarity.	1-pound can $4.95	$0.31
Nutri-1000 (Syntex)	Skim milk, corn oil, sucrose, corn syrup solids	Liquid	Not required	1,060	40.3	55.0	101	Supplemental nourishment	Chocolate and vanilla flavors available; low sodium supplement.	10-oz can $.81	$0.08
Sustacal (Mead Johnson)	Sucrose, concentrated sweet skim milk, corn syrup solids, soy oil, sodium caseinate, soy protein isolate	Liquid	Not required	1,000	60.0	23.0	137	Supplemental nourishment	Chocolate and vanilla flavors available; high sodium content.	12-oz can $1.09	$0.09
Sustagen (Mead Johnson)	Nonfat milk, corn syrup solids, powdered whole milk	Powder	100 grams powder with 160 cc water. Mix in blender.	1,700	100.0	14.0	284	High-calorie supplemental nourishment	Various flavors available; high sodium content.	1-pound can $4.71	$0.29
Instant Breakfast (Carnation)	Nonfat milk, soy protein, sodium caseinate, sucrose, corn syrup solids	Powder	Mix one package (1.2 oz) with 240 cc water. Mix in blender.	967	57.0	30.0	117	Supplemental nourishment	Various flavors available.	Box of six packages $1.19	$0.17
Ensure (Ross Laboratories)	Corn syrup solids, sucrose, corn oil, calcium caseinate, soy protein isolate	Liquid	Not required	1,060	37.0	37.0	145	Lactose-free supplemental nourishment	Various flavors available; good for individual with lactose intolerance.	8-oz can $.57	$0.07
Flexical (Mead Johnson)	Sucrose, corn syrup solids, enzymatically hydrolyzed casein, soy oil, tapioca starch, medium chain triglycerides	Powder	Mix 2 oz powder with 7 oz water. Mix in blender.	1,000	22.4	34.0	154	Used for patients with problems in digesting and absorbing food nutrients; very low residue	Various flavors available; very high osmolarity.	1-pound can $10.87	$0.68

Precision Low Residue (Doyle)	*Maltodextrin pasteurized egg-white solids, sugar, vegetable oil*	*Powder*	*Mix 3 oz powder (one package) with 240 cc water.*	*1,100*	*20.0*	*0.0*	*249*	*Low-residue nutritionally complete diet*	*Unflavored. Cherry, lemon, lime, orange.*	*Six 3-oz packages $8.70*	*$0.48*
Precision High Nitrogen (Doyle)	Maltodextrin pasteurized egg-white solids, sugar, vegetable oil	Powder	Mix 2.93 oz (one package) with 240 cc water.	1,000	44.0	0.5	218	High-protein low-residue, nutritionally complete diet	Citrus fruit flavor.	Six 2.93-oz packages $16.20	$0.92
Vivonex (Eaton Laboratories)	Pure amino acids, safflower oil, glucose, glucose oligosaccharides	Powder	Mix 2.82 oz (one package) with 250 cc water. Mix in blender.	1,000	20.0	1.4	226	Low-residue nutritionally complete elemental diet	Unflavored Vivonex is highly unpalatable. Flavor packets are available.	Six 2.82-oz packages $11.88	$0.70
Vivonex High Nitrogen (Eaton Laboratories)	Pure amino acids, safflower oil, glucose oligosaccharides	Powder	Mix 2.82 oz (one package) with 250 cc water. Mix in blender.	1,000	45.6	0.9	202	High-protein, low-residue elemental diet	Unflavored Vivonex is very unpalatable. Recommended for tube feeding only.	Six 2.82-oz packages $22.92	$1.35
Citrotein (Doyle)	Sugar, pasteurized egg-white solids, maltodextrin	Powder	Mix one 1.18-oz package with 180 cc water.	660	39.9	1.7	121	Low-fat, low-residue lactose-free, oral supplement	Orange-flavored supplement.	Six 1.18-oz packages $4.50	$0.64
Medium Chain Triglycerides (Mead Johnson)	Fractionated coconut oil	Oil	None required	8,300	0.0	920.0	0	Oral supplement for persons who cannot efficiently digest and absorb conventional long-chain food fats. Given as 1 tbsp three or four times per day or as prescribed by physician. Should be mixed with juices or incorporated into sauces. Recipes available.			
Portagen (Mead Johnson)	Corn syrup solids, medium chain triglycerides	Powder	Mix 7.2 oz powder with 720 cc water.	1,000	33.6	45.7	110	Low-lactose oral feeding for persons with fat intolerance	Unpalatable plain. Should be mixed with fruit juices. Receipes available.	1-pound can $5.46	$0.34

*Approximate retail prices are based on wholesale prices with a one-third markup (50 percent profit). Wholesale prices were obtained from *Drug Topic Red Book, 1977*, copyright Litton Industries, published by Medical Economics Co., Oradell, N.J.

†Liquid ounce or dry measure ounce, depending on form of supplement.

‡All registered trade names.

fast form an extraordinarily important part of the nutritional maintenance of these patients (Tables 1 and 2).

Patients who receive irradiation to the pelvis and abdomen may suffer side effects of malabsorption, diarrhea or obstruction. Low-residue diets or elemental diet preparations are sometimes indicated in order to keep fecal bulk at a minimum. Patients with obstruction may require elemental diets or parenteral nutrition. Milk products must be avoided if temporary lactase deficiency occurs, or Lact-Aid may be used to convert the lactose to lactic acid and permit the use of milk.

The low-residue diet is similar to the standard soft diet in food restrictions. Vegetable juices, cooked whole beets, cooked whole carrots and cooked asparagus tips are allowed. All other vegetables must be pureed. If these measures are ineffective, low-residue diets such as Precision LR and Vivonex* provide complete nutrition and require little digestion. Elemental preparations such as Flexical and Vivonex are generally poorly tolerated when taken by mouth, however, and often require tube feeding. Some supplements are better accepted by patients than others.[22] Cost and availability also vary (Table 2).

Chemotherapy Problems

Chemotherapeutic drugs are an important part of anticancer therapy. These agents frequently cause side effects including nausea, vomiting, anorexia, stomatitis, malabsorption and diarrhea, which lead to nutritional problems.

Antinauseant medications such as prochlorperazine can be given to reduce discomfort and are often effective if taken about half an hour before meals.

Different drugs cause varying degrees of nausea and vomiting. Nausea occurs frequently with nitrogen mustard, the nitrosoureas, adriamycin, cis-platinum, mitomycin-C, vinblastine and streptozotocin; commonly with procarbazine and cyclophosphamide; more rarely with vincristine, prednisone and methotrexate.

Chemotherapy may be given combined with heavy sedation in the evening to decrease the side effects of nausea and vomiting, enabling the patient to escape through sleep the peak hours of discomfort. Many patients increase oral nutritional intake before chemotherapy in order to offset the weight loss that occurs during therapy.

The treatment regimen for stomatitis is a diet consisting of cream soups, cooked cereals, milk shakes, eggnogs, custards, ice cream and juices. Alcohol should be avoided and smoking should be curtailed.

Some measures that often permit moderate oral intake in patients with stomatitis include mouth care with salt and soda washes (made by adding 1 or 2 tablespoons of baking soda and 1 teaspoon of salt to a quart of warm water) or lidocaine hydrochloride (Xylocaine) suspension taken orally; treatment of complicating candida infections, and adequate analgesia. Foods are better tolerated at room temperature or slightly chilled; and fruit nectars are more easily taken than are citrus juices, which may cause a burning sensation.

Supplementing the diet with high-protein, high-calorie liquids is important to the aim of maintaining protein and calorie intake during the time needed for healing and thus promoting the healing process by preventing the malnutrition that would otherwise occur.

Diarrhea should be controlled with proper medication or by avoidance of milk in patients who are temporarily lactase-deficient following therapy. For lactase deficiency Lact-Aid may also be used to convert lactose to lactic acid. After diarrhea has diminished, the patient can take liquids and gradually start soft, bland foods.

Dietary Supplements

In addition to milk shakes and eggnogs, there are many commercial dietary supplements (Tables 1 and 2), and new dietary preparations become available constantly. The limited number of products discussed in this report are those used most frequently for patients treated in the Division of Medical Oncology at Mount Zion Hospital and Medical Center.

Sustagen, Sustacal and Meritene are powdered supplements that are available without prescription in most larger drugstores. They come in various flavors and mix with water or milk. Carnation Instant Breakfast, a powdered supplement available in grocery stores or supermarkets, comes in a variety of flavors and can be mixed either with milk or with half-and-half. Pharmacists can order other supplements that are not routinely stocked. The person who purchases supplements will probably find the prices at larger pharmacies are lower than those charged by small or hospital pharmacies.

*All nutritional supplements mentioned in this paper are registered trade names.

TABLE 3.—*Comparison of Nutritional Supplements*

*Supplement**	*Flavor*	*Mean Rating†*
Ensure	Vanilla	3.19
Nutri-1000 ...	Vanilla	2.93
Sustagen	Vanilla	2.19
Meritene	Vanilla	2.15
Vivonex	Orange	1.80
Precision LR ..	Orange	1.76
Flexical	Vanilla	1.19

*All registered trade names.
†5 = excellent taste; 1 = very poor taste.

While all these products supplement the diet with added nutrients, vitamins, calories and protein, the protein content of many of these drinks can be doubled by mixing with milk reinforced by instant dry nonfat milk solids (a cup of milk solids to a quart of whole milk). This double-strength milk can be used in making cream soups, puddings, custards, milk shakes and many other dishes, as well as in the preparation of supplements.

In a recent study that compared patient acceptance of various oral supplements, Meritene was significantly preferred over elemental diet or low-residue preparations such as Precision LR, Vivonex HN and Standard and W-T Low Residue food.[22] When other preparations were compared, Ensure, Nutri-1000 and Sustacal rated significantly higher than Meritene or Vivonex Standard. In a study we have recently conducted 21 physicians and dietitians participated in a taste test of various dietary supplements. All supplements were coded and blindly scored on a scale from 1 (very poor taste) to 5 (excellent taste). Samples were freshly made and served at room temperature. Results are shown in Table 3. Ensure and Nutri-1000 were significantly favored over Vivonex and Precision LR ($P<.001$). Ensure was not ranked significantly different from Nutri-1000 ($P>.25$), but was favored over all the others ($P<.005$). Nutri-1000 was not significantly different from Meritene ($P>.25$). Meritene was ranked superior to Precision LR ($P<.0025$). Sustagen, Meritene and Vivonex were not rated significantly different from each other ($P>.05$). Statistics were calculated by use of the one-tailed test. There are significant differences in taste between the various dietary supplements tested. Ideally, the chemically defined products would be served as slush or ice or used in recipes designed to improve acceptability to patients. It is important to recognize these taste differences and to switch supplements until an acceptable one is found. Availability and cost also are factors in the choice of a supplement (Table 2), since many of these preparations are not covered by standard medical insurance policies.

Vitamin and Mineral Supplements

There is no conclusive evidence at this time to indicate that decreased or excess amounts of any specific vitamin have beneficial effects in the treatment of cancer in human beings.[23]

Recent attention has focused on the role of trace elements in cancer.[24] Patients with malignancies have decreased levels of zinc in serum,[25] and zinc deficiency may possibly contribute to the decreased sense of taste[26,27] and the immunologic dysfunction in these patients.[28]

The source of vitamins and minerals for human beings should be the food they eat, based on a properly planned diet. For patients who are unable to ingest a normal diet, a preparation containing B complex and C vitamins is generally recommended. Vitamin D is not routinely recommended, since many cancer patients suffer from hypercalcemia.

Other Considerations

Adequate analgesics are essential, since pain contributes greatly to anorexia. Non-nauseating analgesics should be used in adequate dosages based upon individual tolerance.

If ascites is present, the patient may take prescribed diuretics or undergo paracentesis to improve appetite.

Individual eating habits, food preferences and daily eating patterns should be followed as much as possible. If the largest meal is eaten in the morning, this pattern should be continued, with most of the calories taken at that time of day (except perhaps on therapy days).

Mechanical factors such as obstruction have a significant nutritional impact, and malabsorption should be noted early, before significant nutritional imbalance can occur.

The always-encouraging relatives and friends should be told to avoid the entreaty of "just one more bite," and to recognize the limits of the patient. If nutritional status can be maintained, there may not be a progressive decrease in intake in many patients until shortly before death.

It is important to recognize periods when temporary nasogastric, peripheral vein or TPN feedings may be needed for a brief time to maintain a patient during some stressful situation.

Weight can be maintained afterward by reinstitution of oral intake as appetite returns.

No difference or superiority has been shown for natural or organically grown foods when compared with crops grown under standard agricultural conditions with chemical fertilizers.[29] The higher cost of the former may make them less desirable for cancer patients who may be burdened financially.

Cooking with convenience foods may be appreciated as a means to conserve time and energy for patients who live alone or who are unable to shop frequently and prepare food. Frozen-food dinners, canned convenience foods, frozen leftovers and dishes adequate for several meals that are prepared and kept in the freezer until needed, all may help to increase protein and calorie intake. Often the patient's family can help prepare a week's meals to be defrosted and cooked as needed.

Conclusion

Although efforts to maintain proper nutrition may not add significantly to survival, they certainly improve the quality of life. Success depends on improving the caloric and protein intake of patients, often a nearly impossible task that requires the cooperation of the patient, the patient's family and friends and the physician. Those around the patient must constantly devise new ways to add appetizing foods of moderate or high caloric content as many times a day as possible. Eventually, progressive tumor usually precludes effective oral nutritional maintenance.

Profound systemic metabolic changes occur in many patients with cancer and lead to increased energy requirements and cachexia. Nutritional maintenance is an integral part of the treatment of malignancies. The patient must maintain caloric and protein requirements in order to benefit from surgical, medical or radiation treatments. As food intake becomes more deficient, it becomes increasingly difficult to maintain proper nutrition, and starvation occurs. In cachectic patients, the approach we have described will not be effective, and tube feedings or total parenteral nutrition will be required.

Physicians, nurses and dietitians can provide printed materials, present audio tapes and video tapes of discussions about nutrition and conduct diet classes for patients to strengthen further the educational approach to diet maintenance. Doctors can seek consultation with dietitians who are skilled in the nutritional needs of cancer patients. As always, physicians should give patients support, encouragement and feedback. We must strive to prevent the starvation of patients with cancer as long as there is still a chance for curative or palliative treatments.

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Mononuclear Phagocytes: Immunological Functions and Disease Implications

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *It has been our custom to ask our chief medical residents at Moffitt Hospital to discuss a topic at Medical Grand Rounds near the conclusion of their residency year. We have been privileged to have Dr. Lanny J. Rosenwasser as chief resident during this past year.*

DR. ROSSENWASSER:† Cells of mononuclear phagocyte lineage are derived from committed bone marrow precursor cells and are widely dispersed throughout the body. The functions of these cells, complex and as yet incompletely understood, include host defense against microorganisms, interaction with other lymphoid components in the immune response, and removal of necrotic and cellular debris. They also serve as effector cells in the expression of inflammation.

In this staff conference I will review the morphological, kinetic, differentiative and immunobiologic features of these cells. Also some original work will be described which was done during my stay at The National Institutes of Health and concerns the immunologic specificity of macrophages in the expression of thymus derived (T) lymphocyte-mediated immunity. Where relevant, I will try to relate and briefly review the role of these cells in disease processes.

Before proceeding it is necessary to make two points. First, many of the studies I will describe have been done in animal model systems, and while too quick an acceptance of identity between experimental animal and human systems is unwarranted, in instances where correlations can be made, animal and human macrophages have quite similar properties. Second, a number of recent books and reviews have examined the nonimmunologic functions of macrophages,[1-4] and for that reason this review will concentrate on the immunologic role of macrophages.[5-10]

Morphologic, Kinetic and Differentiative Features of the Monocyte-Macrophage Series

The monocyte-macrophage system may be viewed as a continuum of progressively more mature cells, beginning with monoblasts and promonocytes within the bone marrow. Promonocytes

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undergo two or three cell divisions, mature into monocytes and enter the blood where they circulate for a couple of hours. Monocytes migrate into tissues and terminally differentiate into mature macrophages. The tissue distribution of such mature macrophages is described in Table 1. Macrophages may be found freely immigrating onto serosal surfaces, as alveolar macrophages in the lung, as Kupffer cells in the liver, as microglial cells of nervous tissue, as Langerhans cells of epidermis, and as lining macrophages of the lymph node, splenic, and bone marrow sinusoids. In addition, a number of other cell types while not formally proven to be of mononuclear phagocyte origin, have some functions reminiscent of such cells. Examples include the thymus epithelial cell, the synovial lining cell, the osteoclast of bone, and the M cell of gastrointestinal epithelium.

During the progressive maturation of these lines of cells, there is progressive expression of functional, morphologic, and cell surface characteristics which belie the changing capacities of the maturing cells. A summary of these phenomena is presented in Table 2. As the promonocyte matures fully to the most mature tissue macrophage, its proliferative capacity decreases, while by and large its other functional characteristics are increased with maturation; for example, phagocytic capacity, esterase positivity (a measure of lysosomal granules), immunoglobulin fragment C (F_c) receptors, complement receptors and the surface expression of immune-associated (Ia) antigens (a measure of immune competence). Figure 1 shows the morphology of monocyte-macrophages as depicted by a Wright stain of a blood smear (1A), a scanning electromicrograph (1B) and a transmission electromicrograph (1C).

TABLE 1.—*Tissue Distribution of Macrophages or Macrophagelike Cells*

Lining macrophages of the lymph node, splenic and bone marrow sinusoids
Alveolar macrophage of the lung
Kupffer cell of the liver
Freely migrating macrophages of the pleural and peritoneal cavity
Langerhans cell of epidermis
Microglial cell of nervous tissue
Giant cells of granulomata
? Thymus epithelial cell
? Synovial lining cell
? Osteoclast of bone
? M cell of gastrointestinal epithelium

Immunobiologic Functions of Macrophages

The immunobiologic functions of macrophages are summarized in Table 3. Monocytes and macrophages have the capacity for locomotion and diapedesis, useful functions for migrating into tissues and inflammatory sites. Locomotion is directed by a process called chemotaxis, which is defined as the unidirectional migration of cells along a concentration gradient of a chemoattractant. Macrophages also play a significant role in the ingestion and killing of microorganisms. Although polymorphonuclear leukocytes are certainly the first line of defense against pyogenic bacteria, macrophages may kill bacteria via oxygen dependent (hydrogen peroxide, superoxide anions, singlet oxygen and so forth) or oxygen independent (acid, lysozyme, granular cationic proteins and the like) mechanisms. Clearly, however, the macrophage is primarily involved with host defense against facultative intracellular microorganisms such as viruses, mycobacteria, Pneumocystis organisms, toxoplasmas, fungi, and Listeria and Brucella organisms. Additionally, macrophages clear necrotic cellular debris and as such play a role in wound healing. Activated macrophages can be either cytostatic or cytocidal for tumor cells. Macrophages may also control granulopoiesis via production of colony stimulating factor (CSF). Finally macrophages are important

TABLE 2.—*Evolution of Functional Characteristics With Maturation of Mononuclear Phagocyte*

	Promonocyte	*Monocyte*	*Young Tissue Macrophage*	*Mature Tissue Macrophage*
Proliferation	++++*	++	+	0
Phagocyte capacity	+/−	+	+++	++++
Esterase positivity	+	+++	++++	++++
Receptors for F_c portion of Ig	+	++	+++	+++
Complement receptors	++	+++	+++	+++
Surface Ia	++	+++	+++	++

F_c = fragment C Ia = immune-associated antigens Ig = immunoglobulin

*The number of pluses (left to right) indicates increasing or decreasing functional characteristics with maturation.

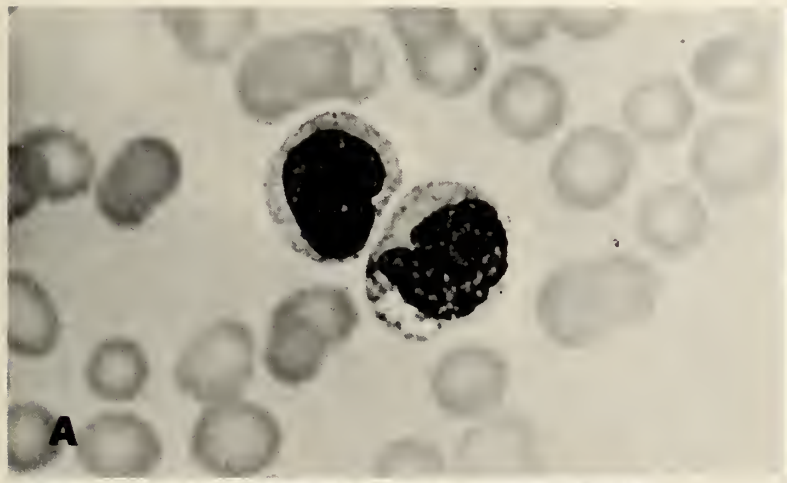
participants in immune reactions, as dealt with in more detail below.

Disease States Associated with the Monocyte-Macrophage Cell Line

There is a wide range of human disorders associated with abnormalities of cells with macrophage-like descendancy. The disorders include mild blood monocytosis (associated with infectious, inflammatory or collagen vascular diseases), neoplastic proliferation of histiocytes (monocytic leukemia, malignant histiocytosis and the like), histiocytic proliferation of unknown origin (such as sarcoidosis, granulomatous vasculitides and Wegener granulomatosis), reactive proliferation secondary to infection (tuberculosis), or chemical exposure (beryllium and zirconium salts), clearly a broad spectrum. Most intriguing, however, are monocyte-macrophage dysfunction syndromes in which subtle defects in macrophage function impair host defense. Random examples of such potential situations are included in Table 4.

Immune Reactions of Macrophages

Macrophages play an active role in both the afferent (inductive) and efferent (effector) limbs of the immune response (Table 5). This area of basic cellular immunology is an area of intense continuing investigation, and more information should certainly be forthcoming in the near future. It suffices to say that macrophages have wide ranging functions in immune responses, including antigen presentation to T lymphocytes and secretion of soluble materials such as prostaglandins, complement components, collagenase, endogenous pyrogen and lymphocyte activating factor (LAF).



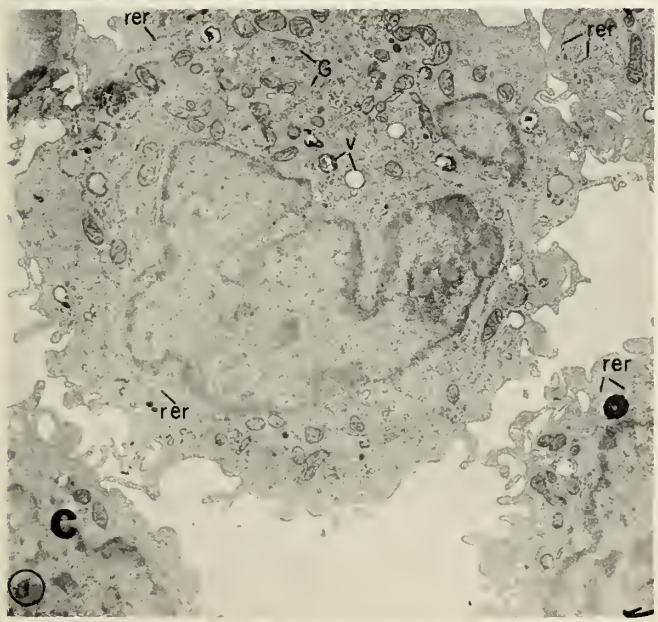


Figure 1.—A, Human peripheral blood monocytes as seen on Wright stain of a blood smear. (Figure provided by Dr. John C. Klock.) **B,** Scanning electron micrograph of adherent human peripheral blood monocyte (note characteristic ruffled membrane). |——| represents 1.0 μm. (Figure provided by Dr. John D. Stobo.) **C,** Transmission electron micrograph of induced rabbit peritoneal exudate macrophage. (Magnification reduced from ×14,000.) V = vacuole, G = Golgi apparatus, rer = rough endoplasmic reticulum. (Figure provided by Dr. Dorothy F. Bainton.)

Not only do macrophages affect lymphocyte function, but certain products of stimulated lymphocytes called lymphokines, also influence macrophage composition, metabolism and functional status. Lymphokines may activate phagocytes such that the activated cell has a greater phagocytic, microbicidal and metabolic capacity. More detailed information concerning immunological reactions of macrophages may be obtained in references 5 through 10.

The bulk of the remaining discussion will concern itself with the precise mechanism whereby macrophages present antigens to sensitized T cells. It is perhaps fitting to begin with some historical perspective. Metchnikoff's classic observations on macrophage phagocytosis were popularized at the turn of the century by George Bernard Shaw in his London stage play *The Doctor's Dilemma.* In contrast to the general public, immunologists did not seriously consider the monocyte macrophage as a major participant in cellular immunity until the early 1960's. The initial excitement about the immunological function of the macrophage stimulated by the proposal that macrophages created an immunogenic RNA-antigen complex was followed by a wave of apathy when initial experiments were not confirmed. However, major advances in our concept of cellular immunology were made possible by corresponding technical advances in *in vitro* methods to assess T cell function. Assays of antigen specific T lymphocyte proliferation *in vitro* as a measure of T cell function (and also as a correlate of *in vivo* delayed hypersensitivity) provided a unique opportunity to dissect the role of the macrophage in immune responses.

Over the past decade our present understanding of macrophage function has evolved from an early generalization that depletion of adherent cells, presumably macrophages, compromised antigen specific T cell proliferation *in vitro.* At least with regard to soluble protein antigens, macrophages seem to have an obligatory role in the antigen specific activation of T cells in both mice and guinea pigs. Macrophages are, in fact, the initial cell to take up protein antigens before their presentation to the immunologically specific T lymphocyte. When briefly exposed to antigen and washed before their addition to populations of macrophage-depleted T lymphocytes from animals primed with that antigen, macrophages will induce T-lymphocyte proliferation equivalent to that of free antigen plus macrophages. This function is not determined by the immune status of the donor macrophage (that is, nonimmune macrophages can present antigen).

These initial studies were followed by two findings which form the foundation for the current model of macrophage-dependent activation of T cells. First, the capacity of antigen-bearing macrophages to initiate T cell activation was not a passive process but was restricted; effective macrophage lymphocyte interaction occurred only when macrophage and lymphocyte shared certain genes that were linked to the major histocompatibility locus (MHC) of the species. Moreover, when T cell responses to antigens, responses which are controlled by the MHC linked immune response

TABLE 3.—*Immunobiologic Functions of Macrophages*

Locomotion and chemotaxis
Ingestion and killing of microorganisms and clearance of cellular debris
Antitumor activity
Control of granulopoiesis
Immune reactions

TABLE 4.—*Monocyte Macrophage Dsyfunction Syndromes*

Disorder	*Potential Macrophage Defect*
Neoplasia	Chemotaxis
Chediak-Higashi syndrome	Abnormal degranulation
Chronic granulomatous disease	Abnormal oxygen metabolism
Hodgkin disease	Neoplastic proliferation of macrophages Suppressor monocytes
Miliary tuberculosis	Suppressor monocytes
Lepromatous leprosy	
Disseminated fungal infection	Chemotaxis Suppressor monocytes
Glucocorticoid treatment	Chemotaxis Microbial killing

TABLE 5.—*Mononuclear Phagocytes in Immune Reactions*

Afferent (Inductive) Limb
Antigen uptake and processing
Antigen presentation to T cells
Intermediate role in the passage of signals to and from lymphocyte subclasses
Interactions with B cells
Secretion of soluble factors
Maintenance of lymphocyte viability and differentiation
Efferent (Effector) Limb
Recruitment into inflammatory reaction of delayed hypersensitivity
Secretion of soluble factors
Phagocytic and biochemical reactions as a consequence of activation

(Ir) genes, are assessed in offspring from a "responder" by "nonresponder" sexual cross, only the responder parental macrophage is effective in eliciting T cell activation. Before these observations were made, immune specificity was felt to be solely a function of the lymphocyte. These studies at least raised the possibility of Ir gene function being expressed in the macrophage.

Insights into the potential mechanisms of action of such Ir genes may be obtained by examining the results of experiments in which insulin is used as a model antigen. The immune response to insulin in mice and guinea pigs is under control of the MHC linked Ir genes. Strain 2 inbred guinea pigs and H-2^b inbred strains of mice recognize an antigenic determinant in the A chain of insulin. In contrast, inbred strain 13 guinea pigs and H-2^d inbred mouse strains recognize an antigenic determinant on the B chain of insulin. Experiments carried out in this system suggested that in offspring of sexual crosses between these two strains of guinea pigs and offspring of sexual crosses between these two strains of mice would after being immunized to insulin, exhibit two distinct clones of T cells: one that recognizes the A chain determinant and is associated with strain 2 guinea pig macrophage or strain H-2^b mouse macrophage I-region gene products, and one that recognizes the B chain determinant and is associated with a strain 13 guinea pig macrophage or a strain H-2^d mouse macrophage I-region gene products. The function of the Ir gene, in both mice and guinea pigs, appears to be to select discrete regions within the antigen molecule for recognition by the T cell. Moreover, this function operates at the level of the macrophage. The further implications of these findings are found in Table 6.

TABLE 6.—*Implications of Studies Using Insulin as a Model Antigen*

Different inbred strains of animals (or different human individuals) respond to the same complex antigen by reacting to different antigenic determinants within the complex antigen
The response to specific antigenic determinants is controlled by specific immune response (Ir) genes tightly linked to the species MHC (HLA in humans, H-2 in mice)
Such Ir genes may be expressed within antigen presenting cells (cells of mononuclear phagocyte lineage)
The mechanism of such macrophage mediated Ir gene function involves the selection of discrete regions within the complex antigen for recognition by immune T cells

MHC = major histocompatability locus

TABLE 7.—*Potential Roles of Macrophages in Mediating Human Disease*

Disease states with associated defects in T cell mediated immunity may in part be due to subtle defects in macrophage function
Examples of diseases or pathological conditions which suggest a confluence of antigen, mononuclear phagocyte, lymphocyte and possibly major histocompatability locus
Insulin allergy and resistance
Drug allergy
Methyldopa (Aldomet) induced hemolytic anemia
Procainamide-induced systemic lupus erythematosus
Ragweed allergy
Gluten sensitive enteropathy and dermatitis herpetiformis
Paget disease
Sjogren syndrome
Juvenile onset diabetes mellitus
Graves disease

Speculation on the Relationship of the Immunologic Function of Macrophages to Human Disease

What relevance then, if any, do these observations have to human physiology and pathophysiology? The first portion of Table 7 suggests that diseases, which heretofore had been thought of as disease with defects in cell-mediated immunity or T cell mediated immunity, may in fact be due to subtle defects in macrophage function.

Furthermore, as outlined in Table 7, there are a number of conditions in which there exist a confluence of MHC, theoretical antigen, sensitized lymphocyte and macrophage, suggesting that the initiation of the pathogenic mechanism may depend upon a macrophage mediated event.

It is apparent that further studies of macrophage function and malfunction will likely provide important information for our understanding of normal immunity and of human diseases.

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Important Advances in Clinical Medicine

Epitomes of Progress—Dermatology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in dermatology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in dermatology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Dermatology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Current Status of Retinoic Acid and Benzoyl Peroxide in the Treatment of Acne

USED CORRECTLY, combination topical therapy with retinoic acid and benzoyl peroxide applied respectively in the evening and the morning has been a significant addition to the agents available for the treatment of mild to severe forms of acne, either alone or as adjunctive therapy.

Retinoic acid increases epidermal surface and follicular duct wall turnover and decreases the cohesiveness of the horny cells produced by these epithelia. In turn, this reduces the formation of comedones in the follicular duct and decreases the thickness of the epidermal and follicular duct stratum corneum, which may enhance transepidermal and transfollicular penetration. This would tend to increase the concentration of agents such as topical and systemic antibiotics in the vital intrafollicular duct location where the first morphologic evidence of acne is seen as a retained, increased horny layer.

Benzoyl peroxide appears to have a comedolytic effect similar to that described above for retinoic acid, but to a much lesser degree. In addition, it appears to reduce free fatty acids in skin surface lipid, probably primarily as a result of the reduction in Propionibacterium acnes, which have been implicated in a variety of possible ways (see epitome by Puhvel in this issue) in the etiopathogenesis of acne.

It also has been suggested that benzoyl peroxide may act to reduce the irritability of the skin produced by retinoic acid by tending to produce a thickening of the stratum corneum, counteracting the thining produced by retinoic acid.

Recently, conflicting and as yet incomplete studies of the combined application of retinoic acid and ultraviolet light on the skin of albino hairless mice have shown that under some circumstances the retinoic acid appeared to act to accelerate the appearance of and increase the number of squamous cell carcinomas produced whereas under others it appeared to act as a protective factor, reducing the incidence of ultraviolet-induced skin cancer in these mice. Retinoic acid itself is not carcinogenic.

Until the issue is more fully resolved and it can be determined whether these conflicting findings do in fact have any relevance to the clinical use of retinoic acid in humans whose skin is

grossly different from that of albino hairless mice in structure and function, it would appear wise to follow the recommendations of the Ad Hoc Committee of the American Academy of Dermatology. These include minimizing sun exposure and avoiding use of retinoic acid in the presence of sunburn until fully recovered, as described in the package inserts for the drug. Patients with chronic sun exposure, genetic predisposition to sunlight-induced skin cancer or unusual susceptibility to sun-induced skin damage should be particularly cautious when using retinoic acid. I would reemphasize that at this time the data are incomplete and inconclusive, and may or may not apply to human use situations. However, they cannot be ignored and strict adherence to the recommendations noted above coupled with an awareness of new developments as they evolve will allow physicians maximum latitude in selecting therapy suitable to a patient's needs while vigilantly protecting the patient's best interest.

RONALD M. REISNER, MD

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A Possible Influence of Topical Retinoic Acid on Sunlight Induced Cancer—Report of the Ad Hoc Committee of the American Academy of Dermatology. Evanston, IL, American Academy of Dermatology, Jul 1978

Epstein JH: Retinoic acid and experimental carcinogenesis. Read before the Pacific Dermatologic Association, Coronado, CA, Sep 18, 1978

New Concepts in Pathogenesis of Acne

ACNE is a multifactorial disease in which hormonal, biochemical, microbiological and immunologic factors interplay. The most widely accepted theory on the pathogenesis of acne is the free fatty acid theory. According to it, the follicular bacteria, particularly Propionibacterium acnes, produce lipases which hydrolyse sebaceous tryglycerides to free fatty acids (FFA) which in turn produce inflammation.

Arguments against the role of FFA are that no significant differences are observed between patients with acne and controls in (1) the free fatty acid content of skin surface lipids, (2) the sensitivity of skin to irritant effects of free fatty acids, (3) density of bacteria in isolated sebaceous follicles of acne prone areas of skin and (4) lipolytic activity of strains of P. acnes. Recently, it has been shown that FFA are not inflammatory when injected into normal human skin. The possible explanation is that the earlier studies injected nonphysiologic amounts that did not reflect *in vivo* levels.

Recent studies have found that follicular bacteria, though harmless, may act as primary inflammatory agents in closed comedones. The mechanism of action probably involves the production and accumulation of bacterial cytotaxins and cytotaxigens, as well as direct inflammatory activity of bacteria introduced into the perifollicular dermis following the rupture of the comedonal wall. The successful use of antimicrobial therapy in the treatment of inflammatory acne substantiates their role as causative agents. The mechanisms whereby bacteria produce the inflammatory reaction remain controversial and unclear.

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Role of Hepatitis Virus in Gianotti-Crosti Syndrome

PAPULAR ACRODERMATITIS OF CHILDHOOD (PAC) or Gianotti-Crosti syndrome is a transient nonpruritic papular dermatitis manifesting as monomorphous flat eyrthematous or flesh colored lichenoid papules occasionally scaly, with a predilection for extensor surfaces. It has been reported from infancy to early teens but is commonly seen in two- to five-year-old children, with equal sex incidence. Associated features include lymphadenopathy, malaise, fever and diarrhea. The lesions disappear within six weeks but can persist longer. On microscopic studies mononuclear cells and histiocytes are seen in the reticular dermis and perivascular spaces.

Nearly all patients have acute hepatitis which is usually anicteric and indistinguishable from viral hepatitis. During the acute phase of the disease, all patients have hepatitis B surface antigen in the serum with elevated serum transaminases. During the convalescent phase, three

months later, patients are found to have anti-hepatitis B core antibody in their sera. Antibody responses to the hepatitis B core antigen and surface antigen are identical in patients with viral hepatitis and PAC. These findings have suggested the hypothesis that PAC may be a manifestation of the primary infection with hepatitis B virus. PAC can progress to chronic active liver and serologic abnormalities may persist for several months. However, the hepatitis B surface antigen or e antigen has not been isolated from the skin.

The infectivity rate is low. Hepatitis B virus antigen has been found in sera of siblings and parents of patients many months after exposure.

Patients with infantile papular acrodermatitis have clinical similarity but lack evidence of liver disease and lymphadenopathy.

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Colombo M, Gerber MA, Vernace SJ, et al: Immune response to hepatitis B virus in children with papular acrodermatitis. Gastroenterology 73:1103-1106, Nov 1977

Topical Corticosteroid Therapy

TOPICAL GLUCOCORTICOSTEROIDS are among the most frequently prescribed topical agents for an inordinate variety of cutaneous conditions by physicians in practically every discipline of medicine. Their striking, beneficial effects are reflected by the proliferating array of creams, lotions, ointments and gels containing such agents that is available to physicians. The prolonged and injudicious use of such agents, however, may result in a variety of disturbing side effects. These include the development of rosacea, steroid acne, perioral dermatitis, telangiectasia, stress, atrophy, hypopigmentation, hirsutism and purpura, and enhancement of infections. These adverse effects can result from the use of any of the topical steroid preparations but have been most frequently encountered with the use of the more potent fluorinated glucocorticosteroids.

The strong topical formulations of glucocorticosteroids currently available and new more potent ones appearing on the horizon demand the intelligent use of these agents if these serious side effects are to be avoided. Stoughton has classified the currently available commercial topical glucocorticosteroid preparations into six groups, in respect to their potency. The science of the use of topical glucocorticosteroids involves the selection of the correct strength corticosteroid in the proper formulation for the particular disease process and the particular area of the body involved. The most potent topical steroid preparations are used as a part of the initial therapy for recalcitrant types of dermatoses or when a physician wants to obtain a brisk response.

Once suppression has been achieved, these agents should be replaced by less potent steroid preparations for the purpose of tapering off the topical agents or obtaining the least potent agent which will still be effective therapeutically. They should not be used over a long period. All areas of the body do not absorb steroids to the same degree. The face, scrotum, penis, groin and perianal areas have unique absorptive properties which tend to predispose these areas to the development of undesirable reactions. Further, if steroids are applied under occlusive dressing, such as Saran Wrap, absorption may be enhanced a hundredfold.

Therapists must be constantly alert for the earliest signs of evolving side effects. Open-ended prescriptions for these agents should never be given.

Reflecting the current misuse of topical steroids is the increasing number of patients seen in dermatological offices with conditions resulting from the unskillful use of topical steroid preparations. As Stoughton has noted, "The uneducated and inexperienced have no place in the management of dermatoses with topical glucocorticosteroids."

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Role of Antibody Titer in Pemphigus

PEMPHIGUS is a vesiculo-bullous autoimmune disease of the skin characterized by the presence of an antibody against the intercellular substance of the epidermis. The antibody is bound *in vivo* at the site of the pathologic condition and is present in the serum. It is composed of all four classes

of IgG and binds complement via the classical and alternate pathology of complement. Acantholytic lesions typical of pemphigus can be produced in skin explants cultured in media enriched with pemphigus serum.

Several studies have shown that in most cases, during the acute phase of the disease, the titer of antibody in the serum correlates with the extent and severity of the disease. Therefore, patients without measurable antibody level have minimal disease while patients with high titers have widespread disease.

Controversy exists about the role and the benefit of following the antibody titer as a guide to therapy. Recent studies of clinical status in patients have shown that a rise in titer is associated with an exacerbation. Numerous cases are cited in the literature to indicate that clinical usefulness of sequential titers as a guide in therapy is still controversial. They feel that changes in clinical status are the best determinants of therapeutic maneuvers.

There are several reasons that can explain the discrepancy in results. The timing of the sequential serum specimens is not the same in all studies. None of the studies have shown correlation between *in vivo* tissue bound antibody and disease free state. Finally, in different studies different drugs have been used. The data become difficult to interpret because different immunosuppressive agents act differently and alter the immune response. Most studies have not used large enough numbers of patients for sound statistical analyses.

Whether the antibody titer remains a useful guide to monitor therapy for a group of patients is still uncertain. However, for a particular patient a twofold rise or fall in the antibody titer is significant, depending on the dynamics of the immune response. In most patients these changes occur simultaneously with changes in clinical status. In some patients the antibody changes occur before or after changes in clinical status.

The importance and the value of the pemphigus antibody cannot be denied. It is very specific for pemphigus and is present in virtually all cases. It may occasionally be absent due to species or organ specificity of the antibody, prozone phenomenon, interference with other antibodies or error in technique. Pemphigus-like antibodies, are seen transiently in low titers in patients with burns, fungal infections, systemic lupus erythematosus (SLE), myesthenia gravis, toxic epidermal necrolyses (TEN) and drug eruptions, and cross-react with blood group substances.

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Mucocutaneous Lymph Node Syndrome

THE MUCOCUTANEOUS LYMPH NODE SYNDROME (MLNS) was first described by Kawasaki in Japan. It has now been reported worldwide. MLNS almost exclusively affects prepubertal children with a peak incidence during the first 18 months with a slight male dominance.

The principal symptom is a spiking fever ranging from 38 to 40°C (100.4 to 104°F), lasting 5 to 20 days and unresponsive to antibiotics. In most cases there is bilateral congestion of the bulbar conjuctiva, dryness, erythema and fissuring of lips, protuberance of the lingual papillae and erythema of the oropharynx. The exanthem typically starts between the third and fifth day of illness and begins as a pronounced erythema of palms and soles with edema and a painful swelling causing limitation of movement. The rash spreads to the trunk in a variable pattern presenting as erythema multiforme, iris-colored lesions or a morbilliform or a scarletiniform eruption. During the second week, a desquamation begins starting at the junction of the skin and nail, extending to fingers, toes and subsequently to the remainder of the body. Significant frequent finding is a unilateral or bilateral nonsuppurative cervical lymphadenopathy of 1.5 cm or greater. Other infrequent clinical features are diarrhea, arthritis, mild hepatitis with jaundice, aseptic meningitis and carditis.

No specific laboratory test is diagnostic. Commonly, a leucocytosis with a left shift increased sedimentation rate and rarely elevated IgE is seen.

The mortality rate is about 1 to 2 percent. Death is frequent in children when cardiac com-

plications develop. Autopsy findings show that arteritis involving most major blood vessels is the primary histologic change. Identical lesions are seen in infantile polyarteritis nodosa. The cause is unknown at present.

MLNS must be clinically differentiated from scarlet fever, juvenile rheumatoid arthritis, systemic lupus erythematosus, erythema multiforme and childhood viral syndromes. There is no specific treatment. Some authors have suggested use of steroids while others recommend use of azathioprine with steroids.

RANDAL COVERMAN, MD

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Langerhans Cell—Epidermal Macrophage

THE MAMMALIAN EPIDERMIS consists of three major cell types: the keratinocytes, responsible for keratinization; the malanocytes that produce and distribute pigment within the epidermis, and the Langerhans cells (LC). The LC cannot be easily visualized under light microscopy on routine hematoxylin eosin staining and require special stains. They have characteristic and distinct features on electron microscopy.

No specific role was assigned to LC for many years. Several elegant studies have conclusively shown that Langerhans cells are members of the monocyte-macrophage-histiocyte system. They share with them common morphologic and physiologic features.

Like macrophages, LC have surface receptors for the Fc portions of IgG and C3 receptors. They have only a moderate phagocytic potential. Cells in the dermal infiltrate of histiocytosis-X have similar surface markers. LC do not form E rosettes or bear surface immunoglobulins and, therefore, do not resemble lymphocytes morphologically.

Initiation of T-cell reponse is an important function of macrophages. They play an important role in the processing of the antigen and effectively present immunologically active moieties to T lymphocytes. This interaction may be achieved by the generation of a soluble signal or by direct cell to cell interaction. In the latter method, in the first step, a nonspecific binding occurs. During the second step, a binding occurs which is antigen dependent, not easily reversible and eventuates in a proliferation of bound T lymphocytes. Evidence has accumulated to suggest that this macrophage-lymphocyte interaction is regulated and restricted by gene products linked to the major histocompatibility complex (MHC) which are under the control of the autosomal dominant immune response gene. Several experimental studies have shown that these genes code for the Ia antigens present on cell surface. Homology between these structures is necessary for effective cellular interaction.

Recent studies have shown that Langerhans cells bear Ia antigens. Like macrophages, they process antigens, present them to lymphocytes, evoke a blastogenic response and have a stimulating capacity in mixed leucocyte cultures (MLR). Abrogation of these functions by treatment with anti-Ia antisera further substantiates these functions.

These new discoveries on the genetically restricted antigen processing function of the Langerhans cell will add to our better understanding of contact dermatitis while their stimulatory capacity in MLR should have a considerable impact in the field of skin transplantation.

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DNCB—Useful New Compound

DINITROCHLOROBENZENE (1-chloro 2,4-dinitrobenzene) (DNCB) is a simple compound that has become increasingly useful in medicine. It functions as a hapten and consequently becomes a complete antigen when attached to a carrier protein. Approximately 95 percent to 97 percent of the population can be sensitized to it at high concentrations and subsequently develop allergic

contact dermatitis on reexposure at weaker concentrations.

DNCB is a useful tool in studying the immune system. Those patients with a variety of malignant conditions who do not get sensitized to DNCB seem to have poor prognosis. Conversion from reactivity to anergy is often associated with recurrence of malignancy. The commonest method of sensitization involves application of 2,000 μg of DNCB dissolved in acetone applied to 3 sq cm of skin, air-dried and covered for 48 hours. An eczematous reaction develops and lasts a few days. Two weeks later several concentrations of the liquid or creams (or both) are applied on the forearm and examined 48 hours later for erythema and vesiculation, as a positive reaction. Treatment is quite specific and reactions occur only at sites of lesions with sparing of normal skin. A combination of immunotherapy and chemotherapy is more effective than either modality alone.

DNCB has become a very useful tool in topical immunotherapy. It has been reported to be of great benefit in patients with multiple basal cell carcinomas, mycosis fungoides, Bowen disease, xeroderma pigmentosum, nevoid basal cell syndrome, chronic arsenic exposure and chronic radiation dermatitis. It is particularly useful in patients with multiple tumors in whom surgical excision, curettage and desiccation, cryosurgery or radiation therapy is not practical or can cause cosmetic defects. In one series of patients followed over five years, 90 percent cure rates have been reported. There is evidence to suggest that immunotherapy may be of prophylactic value in preventing new basal cell epitheliomas from developing and in bringing about regression of tumor metastasis.

DNCB has been found to be very effective in the treatment of refractory plantar warts, multiple flat warts and other warts resistant and recalcitrant to conventional therapy. The newest therapeutic use for DNCB is in the treatment of alopecia areata. In most studies, regrowth of hair has occurred in 60 percent to 70 percent of patients.

Complication and adverse reaction to DNCB therapy are few and rare. A generalized autosensitization has occurred in a few patients and responds well to systemic steroids. Local reaction may occasionally cause sloughing and leave postinflammatory hyperpigmentation.

In the years to come we may see other applications of this simple but useful compound.

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Photochemotherapy of Skin Diseases

PHOTOCHEMOTHERAPY is the combination of long wavelength ultraviolet light (UVA) and the photosensitizing group of drugs psoralen (P). It is, therefore, also referred to as PUVA. The therapeutic regimen usually involves oral administration of methoxsalen about two hours before exposure with UVA. The initial exposure time and amounts are calculated on the basis of skin type of the patient. The usual starting dose is 1½ to 3 joules per sq cm. The lengths of exposure are gradually increased and the frequency is about once every 48 hours. Once maximum benefit is achieved, the patient is placed on a less frequent maintenance plan.

A multicenter study of 1,308 patients with psoriasis showed significant clearing in 88 percent. The regimen should be used only in cases of severe or extensive psoriasis that have failed to respond or have quickly relapsed after conventional therapy. PUVA is also helpful in stages 1 and 2 of mycosis fungoides as an alternative treatment. The response in vitiligo to PUVA is slow and variable, pigmentation occurs first in perifollicular areas. Dorsal surfaces specifically on the hand, are usually resistant. Severe forms of lichen planus have also benefited from photochemotherapy. Results in the treatment of extensive atopic dermatitis have not been very encouraging. The details of the mechanism of action are not completely known. PUVA inhibits the DNA synthesis phase of the cell cycle. The psoralen molecule forms a weak linkage between neighboring DNA strands, and in the presence of UVA undergoes a covalent binding, forming nonfunctional single strand photoadducts between thymine and cross-links between pyrimidine base pairs. It is not an approved mode of therapy by the Food and Drug Administration and is still considered

experimental. No serious side effects have been observed. Early side effects of pruritus, erythema and occasional nausea are infrequent. Theoretical long-term side effects of skin carcinogenesis, premature skin aging and ocular problems are being carefully monitored. No hepatic toxicity has been noted. Oral psoralens do not accumulate in the skin or other organs and are largely excreted within 12 hours in the urine.

PUVA offers potential benefit in a wide range of therapeutic applications to several chronic debilitating skin diseases.

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New Concepts in Virology of Warts in Humans

WARTS IN HUMANS are thought to be caused by human papilloma virus (HPA), a DNA virus of the papova group. The acronym papova is derived from the first two letters of the names of the members of the group, the other two being polyoma virus of mice and vacuolative virus of monkeys. HPV is not shown to be oncogenic in man but can produce benign tumors.

Warts present in a variety of clinically different manners. A few examples include filliform warts, flat warts, plantar warts, venereal warts, laryngeal warts and verruca vulgaris. It has been believed for a long time that the same virus is responsible for all of them. Recent studies have shed new light on the virology of warts in humans.

Delap and co-workers have shown that in condyloma acuminatum, DNA preparation did not have the same DNA sequences as HPV and that the virus-like particles were also antigenically different. Viruses isolated from hand warts, studied by restrictive enzyme analysis, showed that nucleotide sequences were different from HPV, which also had different polypeptide sequences in proteins as studied by immunodiffusion and immunofluorescence. Hansen and co-workers extracted DNA from plantar warts and transcribed radioactive complementary RNA using an Escherichia coli polymerase. The newly formed RNA amended specifically with plantar wart DNA and was used as a probe to study other wart virus DNA. While high concentrations of hybridizing DNA were found in plantar warts, the yield in verruca vulgaris was considerably low and negative in condyloma acuminatum and laryngeal warts.

Employing the technique of restrictive enzyme cleavage and polyacrylamide gel separation four types of human papilloma virus have been characterized. Some similarities are present in types 1 and 2 but type 3 and type 4 appear very different. The protein composition of the virus showed two very different proteins, designated types A and B.

These studies tend to support the hypothesis that, indeed, different viruses may be responsible for different warts and thus account for the remarkable heterogeneity in their clinical presentation and their variation in their response to therapy.

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Characterization of Mycosis Fungoides Cells as Helper T Cells

CURRENT THINKING places mycosis fungoides in the category of thymus dependent (T cells) lymphomas. The erythrodermis and leukemic phase, called Sezary syndrome, is also characterized as a T-cell leukemia. Like T cells, cells infiltrating the skin in mycosis fungoides form rosettes with sheep red blood cells, have receptors for anti-T-cell globulin and lack surface immunoglobulins. Furthermore, they undergo blastogenesis when treated with mitogens like phytohemagglutinin or pokeweed mitogen and localize to T-cell zones of lymph nodes and spleens.

Several subsets of T cells have been recently described. T helper cells are those that stimulate and cooperate with B cells in immunoglobulin production. T-cell help may be specific or nonspecific and may be mediated by contact or solu-

ble factors. T suppressors cells stop the process when it reaches its peak effect and thereby maintain homeostasis.

Most recent studies have shown that the Sezary cell is a T helper cell. It has been found that Sezary cells increase immunoglobulin production by 6-fold to 30-fold when added to normal B cells. No suppression was observed at high T cell to B cell ratio. It was concluded, therefore, that neoplastic Sezary cells originated from a subset of T cells programmed exclusively for T helper activity. These findings have been more recently confirmed.

Such studies are significant and important to practicing physicians. They have opened a new avenue of research for treatment of mycosis fungoides and the Sezary syndrome. In both instances, the prognosis is not good.

These new studies would direct attention toward more sophisticated therapeutic endeavors. Examples include generation of specific suppressor cells to offset the helper cells, shifting of helper cells from specific to nonspecific function, and production of agents that will be aimed at antagonizing the subset of T helper cells, its products or its matched B cell.

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A Capsule on Zinc

DEFICIENCY OF ZINC affects several systems of the human body, including the skin. Patients with acrodermatitis enteropathica have low serum levels of zinc and respond dramatically to supplemental zinc. Cutaneous lesions have been described in patients receiving total parenteral nutrition that respond to zinc administration. Several reports have recently appeared in the literature claiming beneficial results from zinc therapy in acne vulgaris, wound and leg ulcer healing, recurrent oral ulcer, taste and smell dysfunction, dark adaptation and furunculosis.

The adult body contains about 2 grams of zinc, 20 percent of which resides in the skin and hair. Normal levels of zinc are 70 to 125 μg per dl in the serum and 300 to 700 μg per 24 hours in urine. Zinc is absorbed primarily from the small intestine. Rich sources are seafoods, red meats and whole grain cereals. Poor suppliers include sugars, nonleafy vegetables and citrus fruits. It is mostly bound to albumin in the serum. It is excreted in the urine and feces.

The functions of zinc have been studied in animals fed zinc deficient diets and in clinical situations in which reduced serum zinc levels have been detected. At the cellular level, it seems to be an integral constituent of several enzymes and affects the plasma membrane stability of protein, lipid and carbohydrate metabolism and and DNA synthesis.

Decreased levels of zinc are associated with growth retardation, inadequate brain development, lethargy, irritability, tremor, cerebral ataxia and poor skeletal development. Abnormalities of spermatogenesis, parturition, lactation and other gonadal functions, taste, smell and wound healing frequently occur in zinc deficiency. An important role has been ascribed to zinc in the function of various aspects of the immune system in man. The World Health Organization recommends that the daily dietary intake of zinc should be 10 to 15 mg for adults and 5 mg for infants. These requirements may be altered in physiologic states such as pregnancy and lactation and in pathologic states such as inflammatory bowel disease, burns, cirrhosis of liver, chronic bacterial and parasitic infections, cystic fibrosis and in patients being treated with long-term hemodialysis, chelating agents and total parenteral nutrition.

Zinc preparations are frequently sold in drug stores and health food stores. The amount of zinc present should be expressed as the elemental amount, for example, 5 mg of zinc sulphate is approximately 1 mg of elemental zinc. The dose in different clinical indications varies. In acrodermatitis enteropathica, 1 mg per kg of body weight per day is recommended. The margin of safety in the therapeutic dose is large, but toxic effects can occur even at low doses. Common side effects are gastrointestinal symptoms. Overdose is asso-

ciated with fever, malaise, dizziness, headaches, anemia and even death. WILLIAM ABRAMOVITS, MD

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Current Antifungal Therapy

CUTANEOUS FUNGAL INFECTIONS are frequently seen in an office based practice. They are mainly treated by topical agents.

Tinea versicolor, caused by Pityrosporum orbiculare (Malassezia furfur), is often treated with 2½ percent selenium sulfide suspension applied for ten minutes a day or overnight initially and less frequently subsequently. Acrisorcin (Akrinol) sodium thiosulfate is also effective.

Superficial mycoses caused most frequently by Trichophyton rubrum, Trichophyton mentagrophytes or Epidermophyton floccosum include tinea pedis, cruris or corporis. Several topical agents may be used successfully. Tolnaftate (Aftate, Tinactin) is a colorless, odorless compound available as a cream, liquid or powder. It has a cure rate of 73 percent to 93 percent and is available over the counter. Haloprogin (Halotex) is available as a 1 percent solution or cream, and applied daily gives 68 percent to 92 percent cure rates. Clotrimazole (Lotrimin) is an imidazole with a wide range of activity against dermatophytes, yeasts, filamentous and dimorphic fungi. Available as a 1 percent solution or cream, it gives a 59 percent to 85 percent cure rate. Miconazole (MicaTin) is also an imidazole and is effective against dermatophytes, yeast and Gram-positive bacteria and gives a 75 percent to 100 percent cure rate. It also has been found effective in the treatment of aspergillosis, coccidioidomycosis and cryptococcal meningitis. Haloprogin, clotrimazole and miconazole are available on prescription only.

Underlying factors which predispose to dermatophyte infection should be corrected. They include excessive perspiration and retention of sweat by tight fitting garments and shoes; obesity, and diabetes mellitus.

Oral administration of griseofulvin should be reserved for patients unresponsive to topical therapy. In its new form, the active ingredient is dispersed as ultramicrosized particles in a polyethylene glycol vehicle (Gris-PEG, Fulvicin-UIF). Since it does not require fat for absorption, it can be taken without meals. The enhanced absorption of the compound usually requires a dose of only 125 mg twice a day. Higher doses may be needed for recalcitrant and refractory infections.

WILLIAM V. R. SHELLOW, MD

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Future of Antiandrogens in Acne

IT IS WELL RECOGNIZED that the responsiveness of the skin to androgens is associated with many common disorders such as hirsutism, male pattern baldness and acne vulgaris. Although alterations in the keratinization and inflammatory reaction in the follicular duct play a role in the pathogenesis of acne, there is fairly good evidence that lipogenesis in the sebaceous gland is necessary for the disease to occur. The primary events in sebaceous gland lipogenesis appear to be controlled by androgens.

Thus, theoretically it would be reasonable to treat acne with topical agents that are antiandrogen in nature. Cyproterone acetate (CPA) has been used in Europe. Its mechanism of action is competition for the androgen receptor on the sebaceous gland cell. While Cunliffe and Pye have reported no success in its topical use, Winkler has reported decreased sebum secretion of sequential use. CPA with ethynol estradiol given orally results in distinct improvement of acne, but no reports on topical use are available. Flutamide is a similar compound which is nonsteroidal and is effective in animal studies, but has not been tried in humans.

Progesterone competitively blocks the conversion of testosterone to dihydrotestosterone, when applied to male pubic skin reduces 5-reductase activity, but does not reduce sebum output. Estrogen in large nonphysiologic doses reduces seba-

ceous gland size and sebum output, but their mechanism of inhibiting androgen action is unclear. Ethinyl estradiol applied topically reduces sebum production.

There are several controversies and some confusion in the literature regarding the activity of topical antiandrogens. These inconsistencies arise from the fact that different vehicles produce different percutaneous absorption, while some substances initially dissolve the antiandrogen, but later crystalize it, or are absorbed too rapidly. In addition, skin bacteria, proteins, lipids and other agents transform the antiandrogens before they reach their site of action, namely the sebaceous gland cells.

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EDITORIALS

Progress in Clinical Nutrition

THIS SPECIAL ISSUE of THE WESTERN JOURNAL OF MEDICINE focuses on recent progress in clinical nutrition. It appears appropriately at a time of growing public and professional interest in this important topic, which most agree has received less attention than it should over the past several decades. The articles in this issue draw attention to a number of areas where there have been fascinating advances of considerable clinical significance, advances of which practitioners, students and even researchers in medicine should be aware. They are evidence that nutrition in humans is coming into its own as an integral part of modern medicine and its armamentarium.

While progress such as that reported in this issue is important and essential for the diagnosis and treatment of clinical abnormalities related to nutrition, it does not yet answer many of the burning questions of the day with respect to such things as carcinogens and other toxins in the food chain, or whether some kind of basic alteration in the diet of Americans will make a significant difference in the wellness and longevity of the citizenry. One senses that we are only at the threshold of what will come to be our knowledge of such subjects and that in the meantime it may be premature to embark on attempting to redesign our national eating habits. Until more of the facts are in hand clinical nutrition should be given an important place in biomedical research, and even now it should be given a much stronger place in medical education at every level.

—MSMW

The Nutritional Status of Patients With Cancer

ELSEWHERE IN THIS ISSUE is an article by Drasin and associates on nutritional maintenance in patients with cancer.

Recognition of malnutrition as a complication of oncologic therapy is occurring more frequently, probably because better methods of enteral and parenteral nutritional rehabilitation are now available. Certain medical and paramedical groups such as head and neck surgeons and dietitians always have been quite cognizant of the importance of nutritional support before, during and after cancer treatment and have taken advantage of the available methods to do so. With the introduction of intravenous hyperalimentation (IVH) as a means of total parenteral nutrition and with the often dramatic results obtained with its use, emphasis on nutrition in almost every field of medicine now exists. Pharmaceutical companies have noted rapidly escalating sales of previously ignored nutritional products, and the rush is now on for them to manufacture cheaper and more effective parenteral products and similar enteral products that are also more palatable.

Practical aspects of nutritional management are being taught in medical schools today and, at least in our school, students are literally clamoring to learn the proper techniques of administering IVH and enteral nutritional supplements. Students are graduating from medical schools with knowledge of the "state of the art" in the field of nutrition and, it is hoped, will demand that the nutritional sciences keep abreast in the area of developmental research. Those of us who are older often must relearn the nutritional biochemistry, physiology and pharmacology taught us in medical schools some years ago and must learn for the first time about the newer parenteral and enteral nutritional rehabilitative techniques. Complications from surgical operations, radiation therapy and chemotherapy are fewer and less severe in well nourished patients than in malnourished ones. The therapeutic margin of safety in malnourished patients is very narrow. Response to chemotherapy appears to be enhanced by a good nutritional status. Leukotactic activity and immunocompetence are restored by nutritionally rehabilitating a malnourished patient, and host repletion occurs as opposed to any observed stimulation of tumor growth. Therefore, it would behoove practicing oncologists to be familiar with the available methods of nutritional maintenance and rehabilitation.

The article by Drasin and his associates is an important addition to the literature, not only

because it is a testimonial to the needs of adequate nutritional management of patients with cancer but also because it gives good advice on how to prepare and present table foods and nutritional supplements so that they are made more appealing and palatable to these patients and are better assimilated. Also, the manuscript has most available nutritional products presented in tabular form listing the ingredients, nutritive value, indications for use and costs. This table is valuable, and I recommend it to readers as a good reference for use when setting up a nutritional plan, the goal of which is to maintain optimum nutrition during oncologic therapy in order to give the patient the best opportunity for response to cancer treatment with minimal morbidity and to improve the quality of life.

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Irrationality in Personal or Public Responsibility for Health

AMONG THE MANY CONFUSIONS that characterize the field of health today are the admitted public responsibility for health on the one hand and a growing determination by many persons to make their own decisions about what will or will not be done in their medical and health care on the other. A variation on this theme is found in a case report, "Scurvy Resulting From a Self-Imposed Diet," in this issue. The report describes the case of a 43-year-old woman who produced serious illness in herself by a self-imposed diet which she continued against the advice of others including her physicians. The illness eventually required admission to hospital for ten days—a situation no doubt resulting in considerable cost and one that might be regarded as a preventable contribution to the rising cost of medical care.

While it may be argued that this patient's illness was mental and that her self-imposed diet was a manifestation of this, the fact remains that scurvy is a preventable illness and that the onset of scurvy was not prevented in this case. Even after good medical advice it was the patient's decision to continue with a self-imposed diet which was inadequate, and the additional fact remains that an unnecessary cost affecting the public was incurred.

These are times of considerable government emphasis on prevention, the government having convinced itself that if this can be accomplished the cost of medical care will be reduced substantially, perhaps even dramatically. This approach has been pursued with some vigor. At first physicians were blamed for not paying enough attention to prevention. More recently an awareness is developing that human behavior and the human environment may have more to do with prevention of human illness than anything else. But it has yet to be realized that as more prevention is achieved, people will remain in the health care system longer, eventually compensating for whatever cost savings prevention may have engendered.

Complex issues of public and personal responsibility for health, health care and prevention are all present in the cited case. Human behavior can and does thwart many, and perhaps most, efforts at controlling health care costs—whether by a person insisting upon deeply inhaling cigarette smoke or driving an automobile recklessly at high speeds, or by assuming one knows best what is good for one's body when such may not be the fact.

Perhaps the lesson to be learned here is that people, whether persons who seek to make their own decisions about their own health, or governments which admittedly have responsibilities for health and for protecting the public purse, do not always behave rationally, particularly when they are convinced that they are right and everyone else is wrong. It is likely in our society that the right of a person to do as he or she wishes with his or her own body will gain more recognition rather than lose it. It is also likely that when poor health decisions are made, wherever, the cost will continue to be shared by all of us. It may just not be possible to curtail health care costs without curtailing health care services which may be needed. Nor is it likely that much can be done about irrationality.

—MSMW

CASE REPORTS

Refer to: Rose M, Greene RM: Cardiovascular complications during prolonged starvation. West J Med 130:170-177, Feb 1979

Cardiovascular Complications During Prolonged Starvation

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PROLONGED STARVATION is an extreme and effective treatment of obesity.[1] In otherwise healthy persons, cardiovascular complications of this treatment have rarely been reported.[2,3,15] Recently a number of cardiac deaths have been associated with fasting modified by liquid protein supplementation.[4,5] We report a case of severe cardiovascular complications that occurred during a prolonged fast unmodified by protein supplements. In this case, endomyocardial biopsy specimens were obtained, and examination of them showed striking pathological findings.

Report of a Case

A 26-year-old woman lawyer whose weight was 90 kg (198 pounds) and height 160 cm (5 ft, 3 in) began a self-imposed fast in September 1977. She first sought medical attention during the following month when she felt well except for a sensation of cold and occasional orthostatic dizziness. Her medical history included psychotherapy for depression. The medical history she gave was judged to be reliable, and she was not taking medications at the time of the fast. Findings on physical examination by one of the authors (M.R.) were normal except for obesity. The electrocardiogram (ECG) showed normal voltage with T wave inversions in V_1 and V_2 which were normal for her age. X-ray studies of the chest showed no abnormalities. Laboratory data are summarized in Table 1.

She made biweekly office visits and continued to feel well while taking nutritional supplements: potassium chloride (40 mEq per day), calcium lactate (1.8 grams per day) and multivitamins with folate (1 mg per day). She drank at least a quart of water a day. The serum potassium level varied between 3.0 mEq per liter and 5.4 mEq per liter. The serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) remained slightly elevated. The blood pressure, which had initially been 100/85 mm of mercury, dropped to 80 mm of mercury palpable without orthostatic changes or tachycardia. By January 1978, she weighed 62 kg (136 pounds) and was unwilling to break the fast despite recommendations that she do so. A week before admission to hospital she started a new job and became physically more active and increasingly fatigued.

On January 17, 1978, her psychiatrist sent her to the emergency room in a taxi because she felt profoundly weak. She denied specific complaints of shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, chest pain or palpitations. On arrival at the hospital she was alert, but blood pressure could not be obtained by cuff or by palpation. The pulse was 130 beats per minute and regular. She was afebrile. Skin turgor was normal and the mucous membranes were moist. The neck veins were full and visible 6 to 8 cm above the sternal angle. The lungs were clear and the heart sounds were distant. A summation gallop was present, and there were no murmurs or pericardial friction rub. The liver was palpable 3 cm below the right costal margin, with a 10- to 12-cm span by percussion, and was nontender and soft. There was no pedal edema and the extremities were cool and dry. Findings on neurological examination were normal.

Laboratory Findings

Blood test findings on admission are summarized in Table 1 under the heading "After Four-Month Fast." X-ray films of the chest showed increased right perihilar markings and a normal

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heart size. The initial ECG (Figure 1) showed a supraventricular tachycardia with aberrant condition of the left bundle branch type (versus ventricular tachycardia) at 130 beats per minute. Two hours later the ECG (Figure 2) showed sinus tachycardia of 100 beats per minute, low voltage of the QRS complexes, prolonged QT interval of 0.40 seconds and absence of the bundle branch block. An echocardiogram (Figure 3) showed decreased septal motion and thickness with an enlarged left ventricular diastolic diameter (LVID) of 5.4 cm (LVID per sq m = 3.3, normal <3.2), enlarged right ventricular diastolic diameter (RVD) of 2.8 cm (RVD per sq m = 1.6, normal <1.4), and decreased velocity of circumferential shortening (V_{cf}) of 0.96 cm (normal >1.05). Arterial blood pH was 7.27, P_{O_2} was 126 mm of mercury and P_{CO_2} was 11 mm of mercury on 4 liters per minute of oxygen administered nasally.

Treatment

In the emergency room, the blood pressure became palpable at 50 mm of mercury after infusion of 1,000 ml of lactated Ringer solution. The patient was transferred to the coronary care unit and a central venous pressure catheter was placed with initial value of 14 cm of water. Digoxin was started but was discontinued after the appearance of sequential premature ventricular beats. On the second hospital day, a Swan-Ganz catheter was inserted. Initial right-sided heart pressures were as follows: right atrium, mean pressure 10 mm of mercury; right ventricle, 30/10 mm of mercury; pulmonary artery, 30/18 mm of mercury (mean,

TABLE 1.—*Laboratory Data for Fasting Patient*

Laboratory Test	*Normal Values*	*After One-Month Fast*	*After Four-Month Fast*
Hematocrit	....	51 percent	36 percent
White blood count	....	14,500 with normal differential	6,300 with normal differential
Platelets	....	Adequate	Adequate
Electrolytes	....	Normal, except K = 3.6 mEq/L	Na = 138 mEq/L, K = 3.7 mEq/L, Cl = 103 mEq/L, and CO_2 = 3 mEq/L
Blood urea nitrogen (BUN)	....	3 mg/dl	4 mg/dl
Uric acid	4.0-8.5 mg/dl	9.3 mg/dl	6.7 mg/dl
Total protein	....	6.4 gm/dl	5.1 gm/dl
Albumin	3.9-5.7 gm/dl	4.2 gm/dl	3.1 gm/dl
Serum calcium	8.7-10.5 mg/dl	10.4 mg/dl	7.5 mg/dl
Serum phosphorus	2.4-4.6 mg/dl	2.7 mg/dl	3.6 mg/dl
Cholesterol	140-225 mg/dl	175 mg/dl	155 mg/dl
Fasting blood glucose	40-115 mg/dl	87 mg/dl	400 mg/dl (on IV solution)
Serum creatinine	0.6-1.4 mg/dl	1.2 mg/dl	1.6 mg/dl
Total bilirubin	0.1-1.4 mg/dl	0.9 mg/dl	2.2 mg/dl
Serum lactic dehydrogenase (LDH)	....	198 mU/ml (normal 60-225 mU/ml)	350 mU/ml (normal 100-230 mU/ml)
Serum glutamic oxaloacetic transaminase (SGOT)	0-41 mU/ml	53 mU/ml	160 mU/ml
Serum glutamic pyruvic transaminase (SGPT)	1-45 mU/ml	65 mU/ml	....
Serum creatine phosphokinase (CPK)	4-51 mU/ml	....	40 mU/ml (serial CPK-MB isoenzymes, less than 5%)
Serum magnesium	1.8-3.0 mg/dl	....	2.1 mg/dl
Serum copper	70-140 μg/dl	....	60 μg/dl
Serum cortisol (fasting)	6-25 μg/dl	....	28 μg/dl
Thyroxine-RIA	5.4-13.0 μg/dl	....	4.8 μg/dl
Thyroid-stimulating hormone (TSH)	<10 μU/ml	....	1.9 μU/ml
Serum folate	4-16 ng/ml	....	4 ng/ml
Vitamin B_{12}	350-1,000 pg/ml	....	1,372 pg/ml
Urine ketones	....	Large	Large
Blood cultures	....	....	Negative
Urine cultures	....	....	Negative
Sputum cultures	....	....	Negative

24 mm), and pulmonary artery wedge (PAW), mean pressure 18 mm of mercury. Oximetry data showed a wide arteriovenous (AV) oxygen difference of 48 ml per liter (normal 30 to 40 ml per liter) and no evidence for an intracardiac shunt.

Hospital Course

For the first seven days, the mean PAW ranged from 12 to 24 mm of mercury and increased notably with small increments of intravenous fluids. The serum potassium levels were as low as 2.4 mEq per liter (day 5) and the serum phosphorus levels became as low at 1.0 mg per dl (day 5). The urine output did not exceed 20 ml per hour for the first nine days unless the patient was given intravenous furosemide in doses up to 200 mg. On the fifth day, the patient remained hypotensive and oliguric. She was willing to consume only small amounts of caloric liquids. On the fifth, sixth and seventh days, she was given

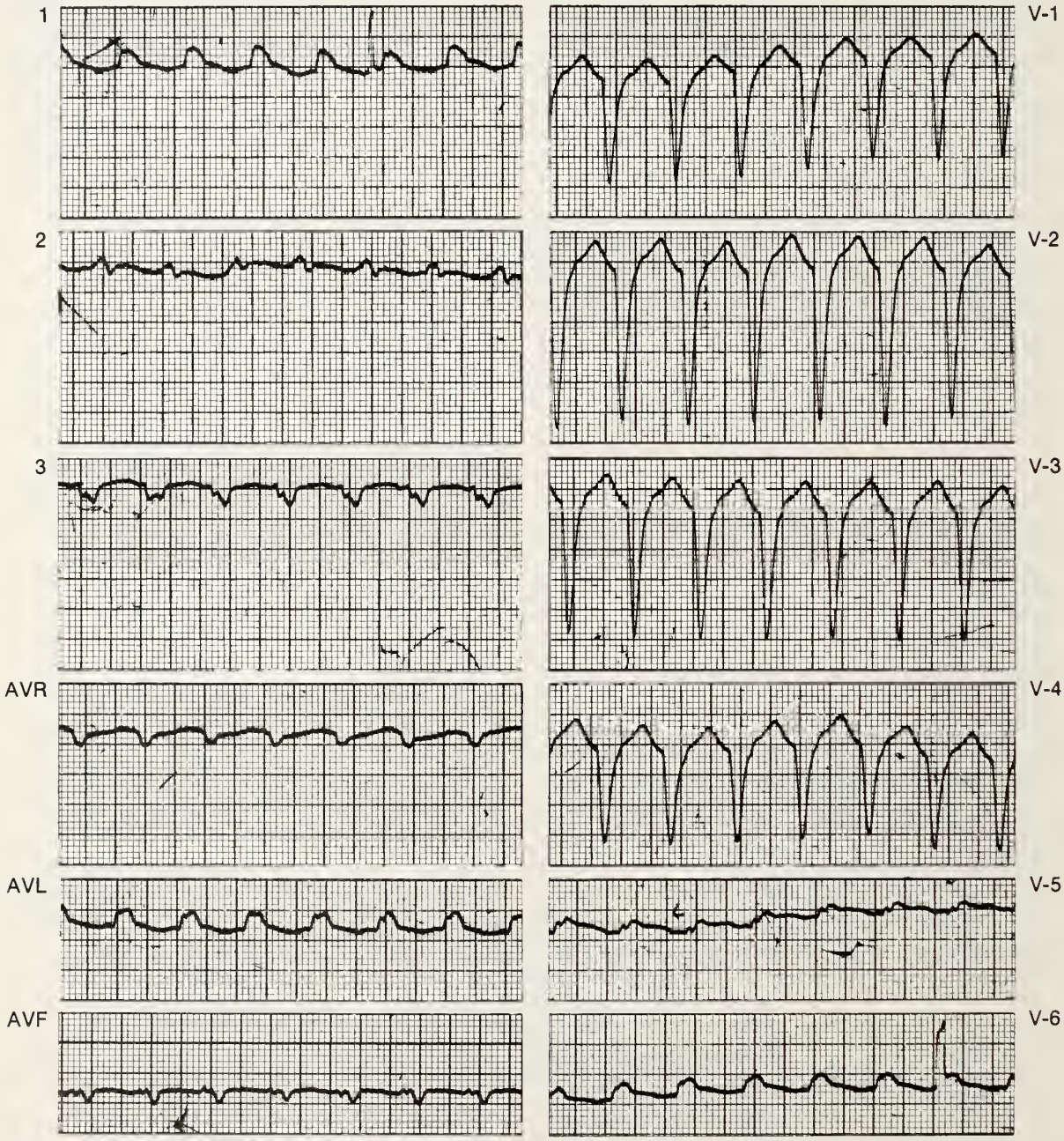

Figure 1.—Initial electrocardiogram showing a supraventricular tachycardia with aberrant conduction of the left bundle branch type (versus ventricular tachycardia) at 130 beats per minute.

intravenous hyperalimentation with Freamine II (McGaw Laboratories, Inc). and Intralipid (Cutter Laboratories, Inc.) totaling 1,300 calories per day. Also, potassium phosphate and one unit of plasma were given intravenously. By the seventh hospital day, the blood pressure did not exceed 70/50 mm of mercury by cuff pressures. The ECG (Figure 4) continued to show low voltages, and new ST-T wave changes and diffuse T wave inversions appeared. Digitalis was administered over the next few days. The blood pressure gradually increased, and by the ninth hospital day the urine output was normal without the use of diuretics.

On the 11th hospital day, three transvenous endomyocardial biopsy specimens were obtained from the right ventricle by previously described techniques.[6] Two of the specimens were adequate for study and were reviewed by the Department of Pathology at Stanford University Hospital. Light microscopy (Figure 5) showed degenerating and vacuolated myocytes, increased areas of fibrosis, compensatory myocyte hypertrophy and focal areas of myocyte necrosis with adjacent mononuclear cell infiltration. These changes were consistent with a nonspecific myocarditis.

On the 13th day, while the patient was on ECG telemetry, an asymptomatic nine-beat episode of ventricular tachycardia at 140 beats per minute was recorded. She was given an oral loading dose of diphenylhydantoin 900 mg, followed by 300 mg per day. Continuous monitoring showed that no further ventricular irritability occurred for the remainder of the hospital stay. In the third week of her hospital stay, the patient resumed eating a 1,500-calorie high-protein diet and continued to improve. A repeat echocardiogram (Figure 6) showed a normal-sized left ventricle with normal wall motion. The discharge ECG showed continued low voltages in the standard leads with diffuse T wave inversions and normal QT interval. After three weeks in hospital, she was discharged on a

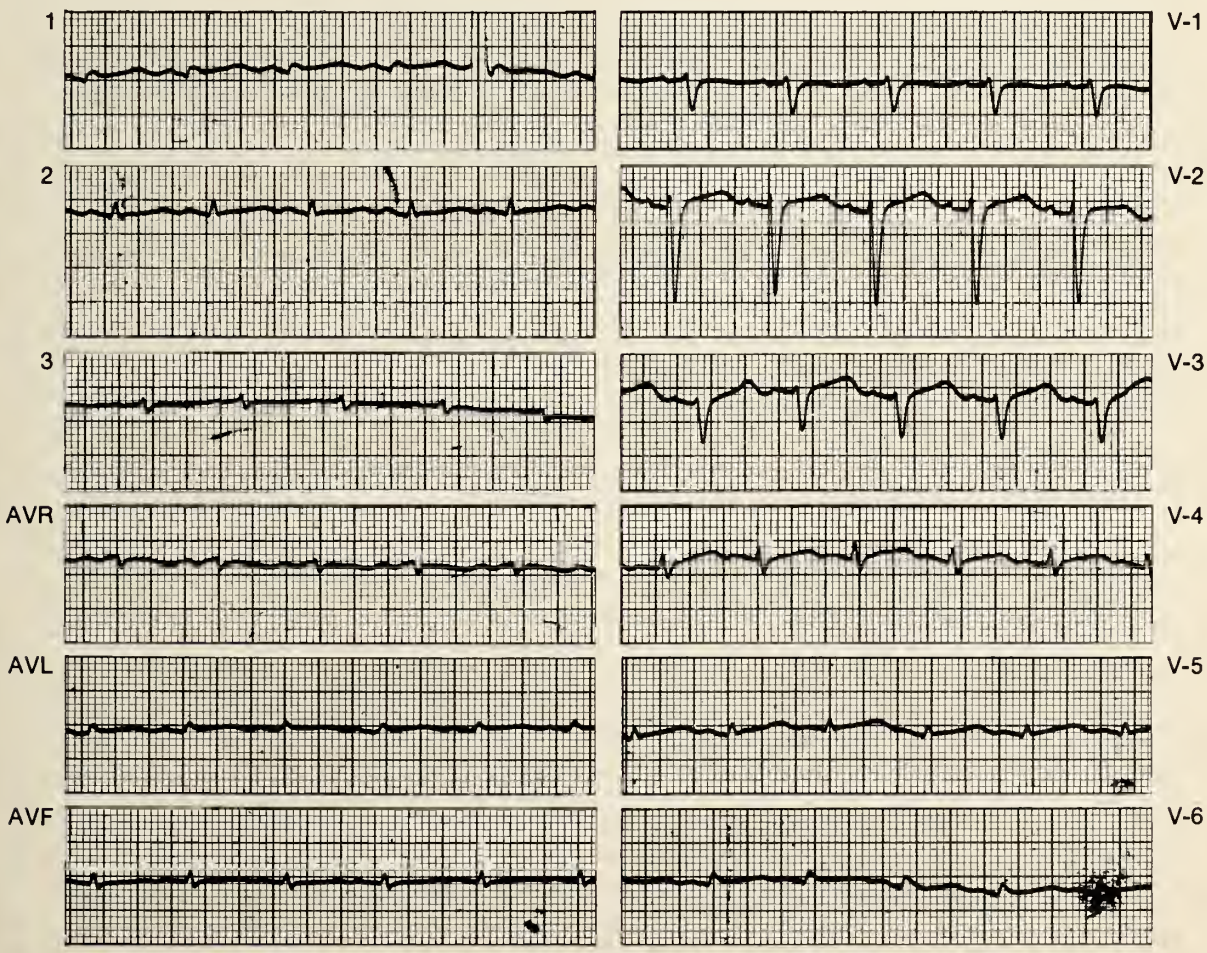

Figure 2.—Two hours later electrocardiogram shows sinus tachycardia 100 beats per minute.

regimen of digoxin, diphenylhydantoin, ferrous sulfate (for a phlebotomy-induced anemia) and multivitamins with copper. Four months after discharge, she had returned to normal activities and was maintaining her weight at 65 kg (143 pounds) on a 1,500-calorie diet. Follow-up studies included a nuclear angiogram three months after discharge which showed mild generalized hypokinesis with a calculated ejection fraction of 0.55 (normal 0.57 to 0.74).

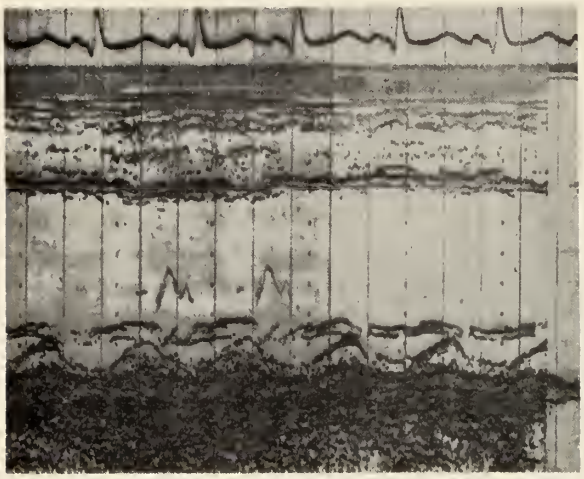

Figure 3.—Echocardiogram with transducer beam directed through the left ventricular cavity showing decreased septal motion and thickness with an enlarged ventricular diastolic diameter.

Discussion

Starvation in nonobese patients is associated with hemodynamic alterations and pathological changes in the heart. The arterial blood pressure, venous pressure and pulse pressure tend to diminish while extracellular volume increases relative to body weight. Keys[7] reported that autopsy showed a reduction in heart size commensurate with the total loss of body weight. Microscopically, there tends to be a decrease in size of the heart muscle fibers followed by evidence of muscle degeneration. Reports of patients with

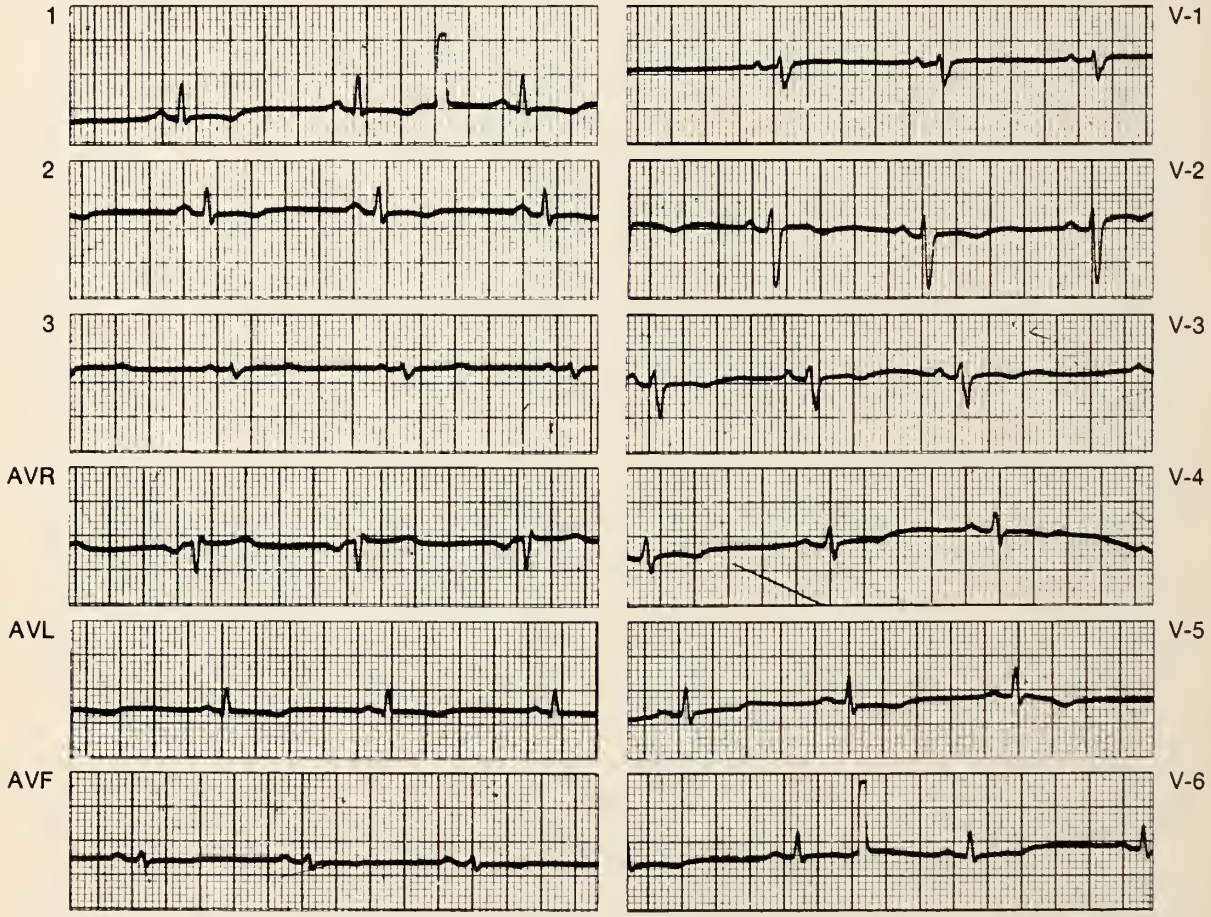

Figure 4.—On the seventh day electrocardiogram shows low voltages and new ST-T wave changes and diffuse T wave inversions.

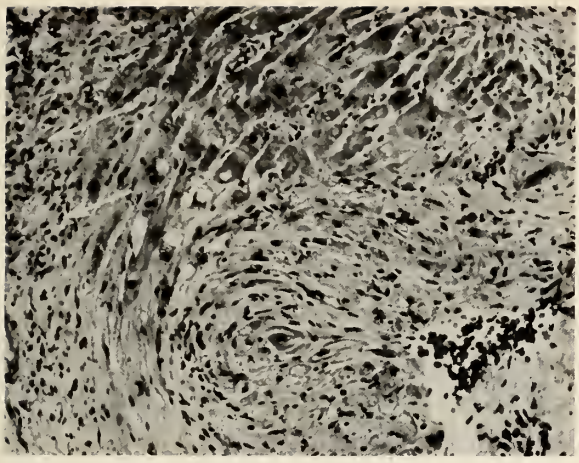

Figure 5.—Right ventricle, endomyocardial biopsy. The arrows show fibrosis with mononuclear cell infiltrates. Adjacent area shows myocyte necrosis and degeneration with compensatory hypertrophy and vacuolation of myocardial fibers. Magnification reduced from ×190.

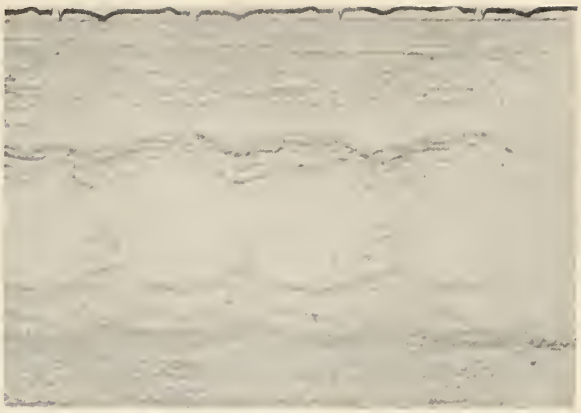

Figure 6.—Echocardiogram with transducer beam directed through the left ventricular cavity at the end of the third week. The septal motion and left ventricular diastolic diameter are normal.

kwashiorkor or marasmus[8-10] have emphasized that the majority have ECG changes often associated with extensive nonspecific myocardial changes discovered by autopsy. Echocardiograms in patients with several forms of wasting diseases have revealed a decreased left ventricular mass (although proportionally less decrease than that of body mass), but normal ejection fraction and velocity of circumferential shortening (V_{cf}).[11]

In previously healthy obese patients, prolonged total starvation has been reportedly well tolerated without complications for periods up to 249 days.[1] However, sudden death as a consequence of total caloric restriction of relatively short duration has been reported in patients with preexisting evidence of heart disease.[12] There are two case reports of cardiovascular complications associated with prolonged starvation in otherwise healthy individuals on metabolic wards. Garnett and co-workers[2] reported the case of a 20-year-old woman who died after 30 weeks of "total starvation" (actually, amino acid supplements were used for at least eight weeks). She died of ventricular fibrillation one week after low-caloric refeeding. The electrocardiogram showed QT interval prolongation in the absence of electrolyte imbalance, or use of antiarrhythmic or diuretic drugs. Postmortem examination of the heart showed a paucity and disruption of cardiac myofibrils only on electron microscopy. Sandhofer and associates[3] reported on a 37-year-old woman who had been on a total fast with vitamin and mineral supplements. Following excessive physical activity, she collapsed due to fatigue and hypotension. The ECG showed sinus tachycardia, low voltages and QT interval prolongation. She was gradually refed, and she made an uneventful recovery. The electrocardiographic abnormalities, however, persisted for 11 weeks.

Recently, a number of sudden cardiac deaths have been reported in otherwise healthy obese people on liquid protein-modified fasts for periods of two to eight months.[4,5] Some had resumed normal diets at the time of death. The ECG's frequently showed prolonged QT intervals and low voltages. Serum potassium levels ranged from 2.1 to 4.1 mEq per liter. Serum calcium, phosphorus and magnesium values were in the low normal range. Autopsy findings in 14 such cases showed evidence of myocarditis in seven and degeneration of myocytes without inflammation in two; documented cause of death was ventricular fibrillation. Anecdotal reports[13] have noted the successful treatment of these arrhythmias with diphenylhydantoin following failure of response to more conventional antiarrhythmic medications.

The pathological findings in our case, obtained from an endomyocardial biopsy specimen from the right ventricle, showed a myocarditis similar to those reported among some users of the liquid protein-modified diets. However, our patient did not receive protein supplements and had fasted four months before admission to hospital. Her weight at time of admission (62 kg or 136 pounds) was consistent with an expected weight loss in total starvation of 1.75 kg per week, but was 12 kg more than her ideal weight of 50 kg (110 pounds). The hemodynamic, echocardiographic

and nuclear angiographic studies suggested biventricular failure due to a congestive cardiomyopathy as evidenced by a wide AV difference, high PAW pressure and left ventricular dilatation and impaired contractility. The oliguria and metabolic acidosis might have been secondary to salt and water retention that occurs with carbohydrate refeeding after starvation or the low cardiac output state (or both). The ECG abnormalities were consistent with a diffuse myocarditis which was substantiated by the endomyocardial biopsy findings. The transient appearance of supraventricular tachycardia with left bundle branch block (or ventricular tachycardia) may have reflected inflammatory involvement of the conduction system, or it may have been secondary to metabolic changes in cardiac conducting mechanisms.

Although associated with starvation, the cause of our patient's heart disease remains uncertain. The elevated liver enzymes are not usually characteristic of prolonged starvation[14] and may have been due to hepatic congestion. There may have been a coincident viral myocarditis; or there may have been a nonspecific inflammatory myocarditis in response to a chemical that was present in, or absent from, this patient's diet. For example, mineral supplements were used in this case and in the cases (resulting in cardiac deaths) reported by Garnett[2] and Sandhofer.[3] However, there were no additional findings of a systemic inflammatory disease, acute and convalescent viral titers were not obtained, and the use of mineral supplements may be only coincidental.

Total body potassium loss is a frequent accompaniment of total fasting.[1-3] Runcie and Thomson[14] reported that 2 of 18 patients after prolonged fasting experienced a "shock-like" state associated with increased levels of sodium and potassium in the urine, which were reversed by refeeding or with potassium chloride. Despite supplemental potassium chloride, several patients spontaneously (and one patient after a carbohydrate load for a glucose tolerance test) developed pronounced hypokalemia as low as 2.4 mEq per liter. In addition, hypokalemic myocardial lesions that have been produced in rats by a potassium-deficient diet[15] resemble the nonspecific myocarditis reported in this case and in some users of liquid protein-modified diets. In man, however, these myocardial lesions are usually reflected in specific hypokalemic electrocardiographic patterns which were absent in this case.

Coronary artery disease in a patient of this age and sex would be unlikely, more so in the absence of chest pain, typical ECG changes, or elevation of the creatine phosphokinase (CPK) myocardial isoenzyme.[16] Hypophosphatemia reportedly retards myocardial stroke work;[17] but there is usually a rapid improvement following phosphate repletion, which did not occur in our patient. Finally, copper deficiency has been associated with myocardial atrophy in animals.[18] In our patient serum copper level was slightly decreased and she received plasma while she was not eating because we hoped to replenish the copper in her serum.

We conclude that the heart may not be spared during prolonged fasting. Serious cardiac damage and death may ensue whether one uses a protein-modified fast or prolonged starvation alone. Close medical supervision on an outpatient basis or observation on a metabolic ward may allow early detection and correction of metabolic abnormalities and myocardial dysfunction that may be precipitated by increased physicial activities or with refeeding. However, even if the patient has continuous ECG monitoring, there may be little protection against the unpredictable onset of serious ventricular arrhythmias and sudden death. Finally, the prognosis for patients who develop endomyocardial biopsy evidence of myocyte destruction during prolonged fasting is unknown.

Summary

Recently a number of cardiac deaths have been associated with fasting modified by liquid protein supplementation. We report a case of a 26-year-old woman who developed biventricular congestive heart failure after having fasted for four months without protein supplementation. Examination of an endomyocardial biopsy specimen showed a nonspecific myocarditis similar to the pathological findings in users of the liquid protein-modified diets. We concluded that serious cardiac damage and death may occur in patients who undertake a prolonged fast with or without liquid protein supplementation.

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Refer to: Walter JF: Scurvy resulting from a self-imposed diet. West J Med 130:177-179, Feb 1979

Scurvy Resulting From a Self-Imposed Diet

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SCURVY IS A RARE disorder usually occurring in older persons who live alone[1,2] or in infants and children secondary to parental ignorance or neglect.[3,4] Occasionally, scurvy can occur in young or middle-aged adults secondary to psychoneurosis and poor eating habits,[5] fad diets,[6] and restricted diets.[7]

We report a case of scurvy in a 43-year-old woman on a self-imposed diet. Early skin and nail changes are presented along with histopathological findings. This patient was initially diagnosed as having allergic vasculitis.

Report of a Case

A 43-year-old woman came to the outpatient clinic of the University of California, San Diego, for evaluation of her skin lesions. She had been followed during the previous three years by private physicians, including a psychiatrist, for complaints of fatigue, weakness, depression, arthralgias and intermittent abdominal pains. No abnormalities had been found and she was felt to have a hypochondriacal neurosis with delusions. However, in September 1977 she noted the development of "red bumps" over the skin of her legs, thighs and arms. Initial evaluation revealed a hemorrhagic skin eruption with splinter hemorrhages of her fingernails and a 6.8-kg weight loss during the previous three months. Blood pressure was 118/70 mm of mercury sitting, and pulse was 96 beats per minute. A diagnosis of allergic vasculitis and possibly a subacute bacterial endocarditis was considered at that time. Results of laboratory tests, including complete blood count, analysis of urine, SMA-12, prothrombin time and partial thromboplastin time, were within normal limits. Venereal Disease Research Laboratories test and tests for rheumatoid factor, antinuclear antibody and cryoglobulins yielded negative results. Serum complement C_3, C_4 and CH_{50} levels were normal. Blood, urine, throat and sputum cultures showed no growth.

Figure 1.—Hyperkeratotic follicular papules with hemorrhage over the anterior thigh. Coiled hairs are present in the follicular plugs.

The patient was seen in consultation at the dermatology clinic. Hyperkeratotic and hemorrhagic papules were noted over both lower and upper

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Figure 2.—Splinter hemorrhages of fingernails in a bandlike configuration.

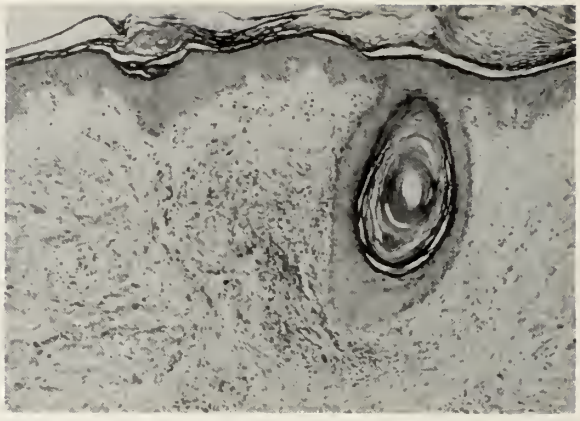

Figure 3.—Follicular keratin plugging with extravasation of red blood cells into the dermis. Note coiled hair cut in cross section in hyperkeratotic follicular orifice. (Hematoxylin and eosin reduced from ×16)

extremities with a few scattered lesions on the trunk (Figure 1). These papules were follicular and perifollicular in location and in appearance were like a hemorrhagic keratosis pilaris. Broken off, coiled-up hairs were found in the hyperkeratotic papules. Fingernails showed bandlike subungual splinter hemorrhages (Figure 2). The patient was edentulous and did not have spongy, swollen or bleeding gums. There was no obvious joint swelling or ecchymosis. A dietary history showed that she had been on an elimination diet during the previous four years because certain "acid" foods caused stomach irritation. She had eaten no fruit or vegetables for the past two years and no meat for three months. Her diet consisted of milk, bread, distilled water, macaroni, spaghetti and pudding. A serum ascorbic acid level was low at 0.4 mg per dl (normal 0.5 to 1.0 mg per dl). Examination of a biopsy specimen from the skin showed a keratin-plugged hair follicle with hyperkeratotic orifice containing a coiled hair (Figure 3). Surrounding the follicle but also scattered between the dermal collagen bundles were extravasated red blood cells with a minimal inflammatory cell infiltrate. There was disruption of collagen formation, especially around the small blood vessels in the dermis. The vessels appeared dilated with thin walls.

The patient refused to supplement her diet with vitamin C. During the next month, hemoglobin and hematocrit values dropped to 7.6 grams per dl and 24 percent, respectively, and weight loss continued. She was admitted to hospital with a blood pressure of 84/50 mm of mercury and a pulse of 140 beats per minute. She now appeared emaciated with a sallow complexion. Results of laboratory tests included serum iron, 50 mg per dl; iron binding capacity, 306 mg per dl; and folate level, 0.6 ng per ml (normal 3 to 51 ng per ml). Leukocyte count was 3,500 per cu mm and red blood cell indices included mean corpuscular volume, 105 cuμ, mean corpuscular hemoglobin, 35 pg, and mean corpuscular hemoglobin concentration, 33 percent. Peripheral blood smear showed pronounced anisocytosis, macrocytosis, hypochromia and hypersegmented neutrophils. Platelets were normal.

The patient was started on a regimen of ascorbic acid, 500 mg twice a day; folic acid, 5 mg twice a day; ferrous sulfate, 300 mg three times a day; and therapeutic multivitamins (Beroca C), 15 ml twice a day, along with psychiatric counseling. Over a ten-day period, her daily dietary intake increased to 2,108 calories, with 108 grams of protein. Her skin, weakness, depression and arthralgias improved significantly and hematocrit value rose to 37 percent over the next two months. Her strength and weight increased although she still refused to eat fresh fruit and vegetables.

Comment

Scurvy is a disorder known from the time of Hippocrates. It was reported in records of the Crusades and became common during the long sea voyages that began in the 15th century. In 1497 and 1498, Portuguese navigator Vasco da Gama lost 100 of 140 sailors to scurvy during his voyage from Portugal to India around the Cape of Good Hope. James Lind in his 1753 publication, *A Treatise of the Scurvy,* established experimentally that sailors with scurvy would have "the most sudden and visible good effects . . . from the

use of oranges and lemons."[8] In 1804, the British Navy made a daily ration of lemon or lime juice compulsory. Thus "limies" as a nickname for British sailors became established.

Ascorbic acid is involved in the hydroxylation of proline and lysine residues in protocollagen to hydroxyproline and hydroxylysine.[9] Collagen is a unique protein because of its high content of these two constituents. In scurvy this hydroxylation process is hindered, resulting in the loss of integrity of collagen fibers. Subsequently, blood vessels lose their support and minor trauma can lead to extravasation of red blood cells and clinical petechiae. Electron microscopic studies of scorbutic human skin have shown changes in fibroblasts and endothelial cells, including a marked decrease of the collagenous component of the dermis with an increase of amorphous to finely fibrillar material.[10]

A review of the literature on the clinical presentation of adult scurvy[2,11,12] reveals that weakness, fatigue, weight loss and arthralgias are common symptoms. Physical findings of hyperkeratotic follicular papules with perifollicular hemorrhages, coiled broken hairs, ecchymosis, swollen bleeding gums and anemia are noted. Splinter hemorrhages of the nails are not frequently reported. Joint effusions, edema and dyspnea appear to be relatively late findings. Folic acid deficiency with megaloblastic anemia and a low leukocyte count has been seen[13] and was evident in our patient. Low blood pressure has been recorded in scorbutic patients and was true for our patient when hospitalized. Evidence from experimental animals suggests that relative adrenal insufficiency may be responsible for this hypotension[14] but this has not been established for humans. Bleeding gums have been associated with scurvy, especially in the interdentate papillae of patients with their own teeth. Our patient was edentulous, and gum changes were not seen. The reason for the development of plugged hyperkeratotic hair follicles in scurvy is not clear. Associated vitimin A deficiency does not seem to be the cause since with experimentally induced scurvy in man hyperkeratotic follicles develop even though the subjects are on vitamin A supplements.[11,15]

Our patient presented with cutaneous signs of scurvy that were diagnostic, including hyperkeratotic follicular papules with coiled hairs and hemorrhage. This occurred on extensor surfaces and was like a hemorrhagic keratosis pilaris. There were also splinter hemorrhages of the nails and associated weakness, depression and arthralgias. Gum changes were not present and apparently are not a helpful diagnostic sign in edentulous patients. Scurvy, though rare, still exists in this day of unusual dietary practices. Early recognition of scorbutic skin changes with associated systemic symptoms can quickly establish the correct diagnosis in a patient who might otherwise present a confusing diagnostic problem.

Summary

Scurvy is a rare disorder that still occurs in this day of unusual dietary practices. A 43-year-old woman developed petechiae, joint pains, weakness and depression on a self-imposed diet containing no fruits or vegetables. Skin findings included a hemorrhagic keratosis pilarislike eruption associated with coiled hairs and splinter hemorrhages of the nails. Skin biopsy showed keratin-plugged hair follicles with decreased perivascular collagen formation and thinning of blood vessel walls resulting in extravasation of red blood cells. These characteristic clinical and histopathological skin findings should suggest scurvy in a patient with concomitant weakness, depression and arthralgias.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Lithium Therapy in Older Patients

TO THE EDITOR: If it is not too late, may I add another note to the correspondence already elicited by the comprehensive article "Lithium Treatment for Psychiatric Disorders" (Maletzky, BM, Shore JH: West J Med 128:488-498, Jun 1978). In an extensive experience (beginning in 1958) with patients receiving long-term lithium therapy, I too have found lithium carbonate a safe prophylactic for manic-depressive illness and unipolar recurrent depressions.

I agree with correspondent Rein Tideiksaar (West J Med 129:147, Aug 1978) that dosages of lithium in the elderly should be reduced, but I would recommend even lower dosages. In these patients, beginning at age 60 or earlier, satisfactory results were usually obtained by dosages of 150 to 600 mg per day, with serum levels of 0.5 to 0.6 mEq or even less.

ESTHER SOMERFELD, MD
Associate Clinical Professor Emeritus
Department of Psychiatry
USC School of Medicine
Los Angeles

More on Wenckebach

TO THE EDITOR: Cabeen, Roberts and Child mention in their thoughtful article "Recognition of the Wenckebach Phenomenon" that Wenckebach first described his eponymic phenomenon from his inspection of pulse tracings (129:521-526, Dec 1978). The history of this discovery is considerably more complex and amazing, particularly when one recalls that the electrocardiograph had not yet been invented.

Theodore Engelmann[1] observed by the naked eye in 1894 that when atrioventricular block in frogs' hearts at times progressively increased, an atrial contraction was not conducted to the ventricle. He demonstrated this to his favorite student, Karel Wenckebach, who described the complicated conduction-defect in man in 1899 from the analysis of radial arteriograms recorded by the polygraph.[2] He reported that Luciani had discovered the phenomenon in frogs' hearts in 1872; so he named it the Luciani period rather than the Engelmann period. However, Wenckebach made it up to his teacher in 1903 by dedicating to him his book on the arrhythmias.

EDWARD SHAPIRO, MD
Beverly Hills, California

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Medical Quality Versus Legal Quality

TO THE EDITOR: In his article in the November 1978 issue, "The Duty of Hospitals and Hospital Medical Staffs to Regulate the Quality of Patient Care," Judge Goldberg points out the frailty of medical policing, but at least the mechanisms exist. As he states, these mechanisms were created by medicine without legal prompting (note his comments regarding the American College of Surgeons). Further, as he points out, medicine is attempting to improve these mechanisms.

On the other hand, he fails to point out that the bar hasn't even started. There are no internal review mechanisms of any kind. A review of the *California Bar Journal* will show that lawyers never lose their licensure for incompetence. Of interest is the fact that under the old law, doctors lost their licensure for improper use of drugs or sexual misconduct, while under present law lawyers only lose licensure for thievery or abandonment. Freudians may have some comments here.

The California Medical Association now has entered more than 20 countersuits against lawyers. These represent reactions to the most egregious examples of poor lawyering. Far more such examples exist, but suits remain unfiled. I am not playing a "gotcha" game. I am dead serious. Poor lawyering costs money to defend against. For physicians these costs ultimately are translated into increased patient costs. Frankly, the societal cost

is enormous for it isn't limited to medical malpractice. Yet no one—neither the bar nor CMA—has dared look at the full scope of the problem.

While the ills of medicine admittedly exist, they are being treated. On the other hand, I would suggest that Judge Goldberg could, as a leader of his profession, contribute by tending to the ills of his profession. He might start by instituting something like the frail systems of internal review currently existing in medicine. Perhaps he could even see what can be done to match law school quality to medical school quality in California. Some two thirds of California law schools are unaccredited. Many are little more than quick buck diploma mills.

Judge Goldberg—heal thyself.

BEN SHWACHMAN, MD, JD
Covina, California

* * *

Judge Goldberg Replies

TO THE EDITOR: As both a doctor and a lawyer, Dr. Shwachman should appreciate the distinction between truth and relevance.

No responsible person whom I know contends that either the medical or legal professions are in perfect order, undeserving of reproach or immune to criticism. But my paper was written in response to an invitation to speak about doctors. I was not asked to speak about lawyers. Therefore the relevant proverb is not Dr. Shwachman's emendation of scripture but Saint Luke's original: "Physician, heal thyself."

B. ABBOTT GOLDBERG, LL B
Judge of the Superior Court, Retired
Sacramento, California

Postzoster Neuralgia

TO THE EDITOR: A comprehensive report on herpes zoster by Dr. James B. Reuler in the December 1978 issue includes the statement that "The major therapeutic challenge facing clinicians is management of postherpetic neuralgia." We feel that postherpetic pain is manageable.

We reported our experience with the use of large doses of vitamin E in the form of d, alpha-tocopheryl acetate up to 1,600 IU daily over a period of several months, if necessary, in a series of 13 patients, during a four-year period, who had suffered from postzoster neuralgia.[1] Of the 13 patients, 11 had had moderate to severe pain for more than six months. Of these, seven had had the pain for more than a year, one for 13 years and one for 19 years. Severity of the pain was estimated by the amounts of analgesics and sedatives required to control it. In nine of the 13 patients there was complete or almost complete relief from pain, in two there was moderate improvement and two thought that they were slightly improved. Of particular significance is the fact that the two patients who had suffered from the neuralgia for 13 and 19 years, respectively, were among those who had complete or almost complete relief.

We have continued to obtain comparable results during the ensuing five years since this report was published, and we also feel that the administration of large doses of d, alpha-tocopheryl acetate during the acute stage of the disease relieves the pain and shortens the duration of the process.

Female hormones and inorganic iron, such as in mineral supplements and white bread or cereals "reinforced" with iron, tend to inactivate vitamin E and should be avoided. Patients with hypertension or badly damaged hearts, or diabetic patients receiving insulin, should be started with much smaller doses, such as 100 IU a day, which can be gradually increased while the blood pressure and the serum glucose levels are monitored to avoid an insulin shock reaction.

Vitamin E properly used in adequate amounts is a simple, effective and nontoxic answer to Dr. Reuler's "therapeutic challenge."

SAMUEL AYRES, JR., MD
RICHARD MIHAN, MD
Los Angeles

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* * *

TO THE EDITOR: I read the article by Dr. James B. Reuler in the December issue of the journal with a minimum of interest and a maximum of amusement. Discussing the treatment of herpes zoster and postzoster neuralgia without mentioning the local subcutaneous injection of triamcinolone in saline is an anachronism. After 44 years in dermatology and the treatment of 400 cases with this modality, I can state with certainty that there is no other treatment that offers the prompt cure of acute zoster, beneficial results in 65 percent of the cases of postzoster neuralgia and the reduction of the latter complication to 2 percent to 3 percent of the cases of zoster treated by this method. These results are far superior to anything mentioned by Dr. Reuler in his article.

I notice that the author endorses the inadequate

studies of Eaglestein, Katz and Brown which, if they prove anything, establish beyond a shadow of a doubt that lactic acid *causes* postzoster neuralgia. I suggest that Dr. Reuler review that article critically.

I hope that you will appreciate and respect my right to criticize an article that is as outdated as Wilbur and Orville's first plane.

ERVIN EPSTEIN, MD
Oakland, California

The Primary Concern

TO THE EDITOR: Are physicians, in their preoccupation with the complexities and costs of modern medicine, losing sight of what has always been thought of as their primary concern: the welfare of their patients?

For example, in the December issue Gray and Leaverton conclude their review on physical child abuse with the comment: "In view of the tremendous expense and inherent difficulty in comprehensive treatment programs, it is our opinion that prevention programs should have the highest priority."

One can muster no more powerful argument in favor of child abuse prevention programs than that children will be less frequently abused, to the extent such programs are successful. That the authors either overlooked this primary concern or did not think it worth a mention is astonishing and disquieting.

AJA LIPAVSKY
San Francisco

More on Cumulative Injury

TO THE EDITOR: Dr. LaDou's article "Cumulative Injury" in the September issue addressed in a balanced manner a vexing problem beginning to emerge as the potential of our compensation system is pressed by claimants' attorneys to its limits —as the latter are obligated by the tenets of their profession to do, in the role of their clients' advocates. The problem is so troublesome, I suggest, because it squarely confronts us with the question of how far we shall accept public liability for individual disability as we increasingly recognize that disease of whatever etiology is the result of a complex interplay of both individual and environmental factors.

Dr. Weissbein's letter in the December issue, however, is another matter entirely. I have no cause to doubt his integrity in evaluating claimants for insurance companies and their attorneys any more than I have to doubt the integrity of those physicians evaluating claimants for their own attorneys. I see nothing more remarkable in the conclusions of the latter that ". . . the job was 'stressful' and aggravated the patient's symptoms or medical complaints . . ." than in his conclusion that ". . . the ailments are really the usual degenerative conditions we all get as we age or the claimants are people who are unhappy with their job, for various reasons." And I see no more reason for considering these physicians as "guns for hire" by plaintiffs than for considering him a "gun for hire" by insurance companies.

Sharing his distress with courtroom battles and mounting legal expenses, for many years I also shared his idea that a panel of medical experts would solve the problem. As I slowly realized, however, that we were probably dealing with physicians of integrity on both sides, I also came to realize that the problem was one of social philosophy, and not medical etiology. The question before the court is the extent to which society shall provide compensation to disabled workers through public or mandated funds, a question cast in the legal language of cause; the question is not one of medical etiology, a multifactorial concept that despite the similarity of words, is very different from legal cause. Obviously, they are not unrelated; to my mind the relationship can best be described by saying that the court considers the medical view of the etiology of a condition as important, but not conclusive evidence, in determining the legal cause of that condition, important but not conclusive, insofar as under compensation law that determination of cause has automatic implications of liability totally unrelated to medical etiology.

The issue is further confused by the still primitive state of medical knowledge concerning the etiology of disease. While as I noted, there is by now a general acceptance of the concept of disease being the result of the interplay of numerous individual and environmental factors, we still lack a language for weighting these factors. All we can say is that they are present; how much significance is attributed to one or another of them is a matter of the individual physician's personal perspective, not presently based in any body of established data. Indeed, we have not even yet an agreed upon operational definition for the concept of "background stress," that level of stress inherent in

existence, a definition crucial to any consensual quantitation of etiological factors in disease.

Given these considerations, it became apparent to me that court appointed experts would not solve this problem. In the first place, by singling out the physician as the court's expert, it would compound the confusion between legal cause and medical etiology by giving the medical testimony unwarranted weight. In the second place, insofar as the physician attributes more or less importance to the various factors that might be involved in the etiology of a disability, the testimony reflects personal bias rather than established knowledge, hardly a satisfactory starting point for the selection of "experts."

While it would certainly not cut the Gordian knot of the problem, within the limits of our adversarial system, I would suggest another solution, one which might reduce the confusion engendered by these two considerations. Recognizing that both claimants and insurance attorneys will turn to physicians whose perspective is similar to theirs, I propose that in contested cases, the court require a simultaneous examination by both physicians to assure that both have access to the same data. After an optional opportunity to discuss the matter, each would prepare a written report to be submitted to the other who would prepare an addendum giving the basis for any differences in conclusions drawn, and the entire package would then be submitted to the court. Should either wish to change the report based on the addendum provided by the other, this should be done without bias; only the final reports and final addenda would be presented to the court.

I recognize that initially this proposal would probably add to the expense of the process, but I suggest that in the long run, it would serve to reduce it. The simultaneous examination and joint access to all data removes the possibility of any differences in facts available to the physicians. The combined reports and addenda define for the court, in advance, what differences in opinion may exist and the basis for these differences, which should reduce the need for prolonged and expensive testimony, and help the court clarify its basis for making or denying awards. To be sure, the approach of a joint evaluation of data by parties likely to come to different conclusions is novel to both the medical and legal settings. Yet there is nothing inherent in either the diagnostic or the adversarial process which precludes it. While it may not solve the problem of mounting costs of awards, insofar as this is to be found in a changing social philosophy, it should reduce the dollar and time costs of the litigation itself.

SIMON L. AUSTER, MD, JD
Contra Costa Medical Services
Martinez, California

* * *

TO THE EDITOR: I read Dr. Weissbein's letter "Cumulative Injury" in the December 1978 issue with interest.

Dr. Weissbein marvels at individuals who claim that "stress and strain" of employment cause heart disease, hypertension, indigestion, nervousness, etc. He believes that the vast majority of claims are unwarranted. He indicates that attorneys suggest that jobs *may* have aggravated conditions and then send patients to doctors of the attorneys' choosing, "invariably one or two or three doctors, always the same ones, no matter what the symptoms are." Finally, he suggests that such doctors should be considered "guns for hire," for lawyers know in advance the conclusions that will be reached "by these so-called impartial consultants."

Dr. Weissbein suggests that a panel of medical *experts* would be the best solution. The courts have repeatedly found that this doesn't work. He suggests that such experts would review all claims and summarily reject those that have no merit, and that this can be done in most cases by reviewing medical records only. But where are such records to come from if a patient is not thoroughly examined? I have had several cases where I have found pathologic conditions while other doctors hadn't even thoroughly assessed the situation. Could Dr. Weissbein's experts make such a finding from incomplete records?

An independent expert may be selected—but that expert does not have the imprimatur of perfection. That expert should be subject to cross-examination. His conclusions may be discarded as not in keeping with the law or with facts that the medical expert may not have had. All parties should have the opportunity to present evidence to the trier of fact, subject to appraisal by others.

Dr. Weissbein may be partially right, that "the situation is entirely out of hand." Part of the reason may be the unwillingness of persons such as Dr. Weissbein to recognize that stress and strain do indeed contribute to human misery and disability.

FRANKLIN DRUCKER, MD
Los Angeles

Refer to: Deger GE, Anderson JA: Control of hypertension in a medium-sized community (Medical Information). West J Med 130:184-187, Feb 1979

Medical Information

Control of Hypertension in a Medium-Sized Community

GRANT E. DEGER, MD
JEANETTE A. ANDERSON, RN
Bellingham, Washington

MODERN ANTIHYPERTENSION THERAPY clearly reduces morbid events.[1-3] National programs against hypertension appear to be working. Two thirds of all persons with hypertension are now aware of their disease and the percentage of patients on adequate therapy has doubled in the past six years. There has been a 50 percent increase in the number of visits to physicians for reasons related to hypertension. Deaths from hypertensive disease are on the decline; stroke and heart disease, which are known to be linked to high blood pressure, continue to decline at a much sharper rate than other categories of cardiovascular disease not related to hypertension. Moreover, mortality rates from stroke, hypertensive disease and coronary heart disease are declining faster in the younger age groups than in the older groups, underscoring the advantage of aggressive preventive therapy.[4]

Physicians and a well informed public are taking more aggressive attitudes toward treatment. Academic fascination with secondary hypertension in the few is giving way to the more pragmatic approach of treating the many.[5-7] Hypertension can be controlled at a minimum cost and it promises to be a high priority item in a society struggling with health care costs.

This report describes how the prevalence of hypertension was reduced in a medium-sized community. Community and private groups worked together effectively in this effort.

From St. Luke's Hypertension Clinic, Bellingham, Washington. Submitted August 24, 1978.

Reprint requests to: Grant E. Deger, MD, Director, Hypertension Clinic St. Luke's Hospital, 809 E. Chestnut St., Bellingham, WA 98255

Methods

Study Area

Whatcom County borders Canada in the northwestern portion of the state of Washington on Puget Sound. Its major city and county seat is the coastal town of Bellingham, population 42,000. Another 51,000 people live in nearby semirural towns, islands and mountainous regions. The people are predominantly Caucasian (98 percent), but include American Indians and Spanish-Americans. Bellingham provides most of the industrial and business activity. Agriculture, fishing, logging and tourism are the other major sources of livelihood in the county.

Community Involvement

The program evolved through several timely occurrences. A physician in private practice was concerned about persons with uncontrolled hypertension who were unaware of their problem. One of our local hospitals was expanding its outpatient services. The hospital offered space, volunteers, supplies, and start-up funds. A staff nurse attended a special hypertension training program geared to nurse practitioners. The hospital planner developed proposals for community involvement. She involved representatives from various community groups including the fire department, school district, Red Cross, hospitals, dietetic association, emergency medical technicians, visiting nurses, community college, council on aging and the health department.

Space, Equipment and Staff

The hypertension clinic was allocated approximately 700 square feet in the basement of the hospital. No significant structural changes were required to accommodate the blood pressure service. Equipment requirements for screening were simple. Standard bladder cuffs (12.5 by 23 cm) with mercury gravity manometers were used. Forms, files and other office supplies cost less than $700.

The clinic is staffed by a physician, a registered nurse, a dietician, a receptionist and unpaid volunteer screeners. The nurse trains the volunteers in techniques of recording blood pressure and of patient guidance and coordinates duty schedules. She oversees the satellite screening stations and maintains a central file of their screening activi-

ties. She also participates in the evaluation and therapy of patients under treatment.

Clinic Structure

The Whatcom County Hypertension Clinic at St. Luke's Hospital began operation as an outpatient service on Thursday, April 24, 1975. The free screening service has always been well received. Approximately 100 persons come to the Thursday 10 AM through 4:30 PM hospital screening each week. Even greater numbers come to our satellite screening sites, which are open on various days at a wider range of hours.

Screening expanded into other community areas including churches, industries, classrooms, city halls, health fairs, and Red Cross and senior citizens' centers. Bellingham firemen screened large numbers of people in their five firehalls. A $3,000 grant by the Washington-Alaska regional medical program supported most of the starting costs and some of the salary of the clinic nurse. Private businesses and persons donated over $400 worth of additional screening equipment as we expanded community activities.

Hundreds of patients found to have hypertension were referred back to their own physicians, while those without a personal physician were treated at the clinic each Thursday afternoon. The hospital dietician was available on referral for a large number of these patients. She involved the spouses in the discussions and paid close attention to followup.

Screening Philosophy

The screening criteria being used for determining the diagnosis of hypertension include the lower or lowest of two or more blood pressure recordings separated by a period of rest. For those 40 years old or less, a diastolic pressure above 90 mm of mercury and for those over 40, a diastolic

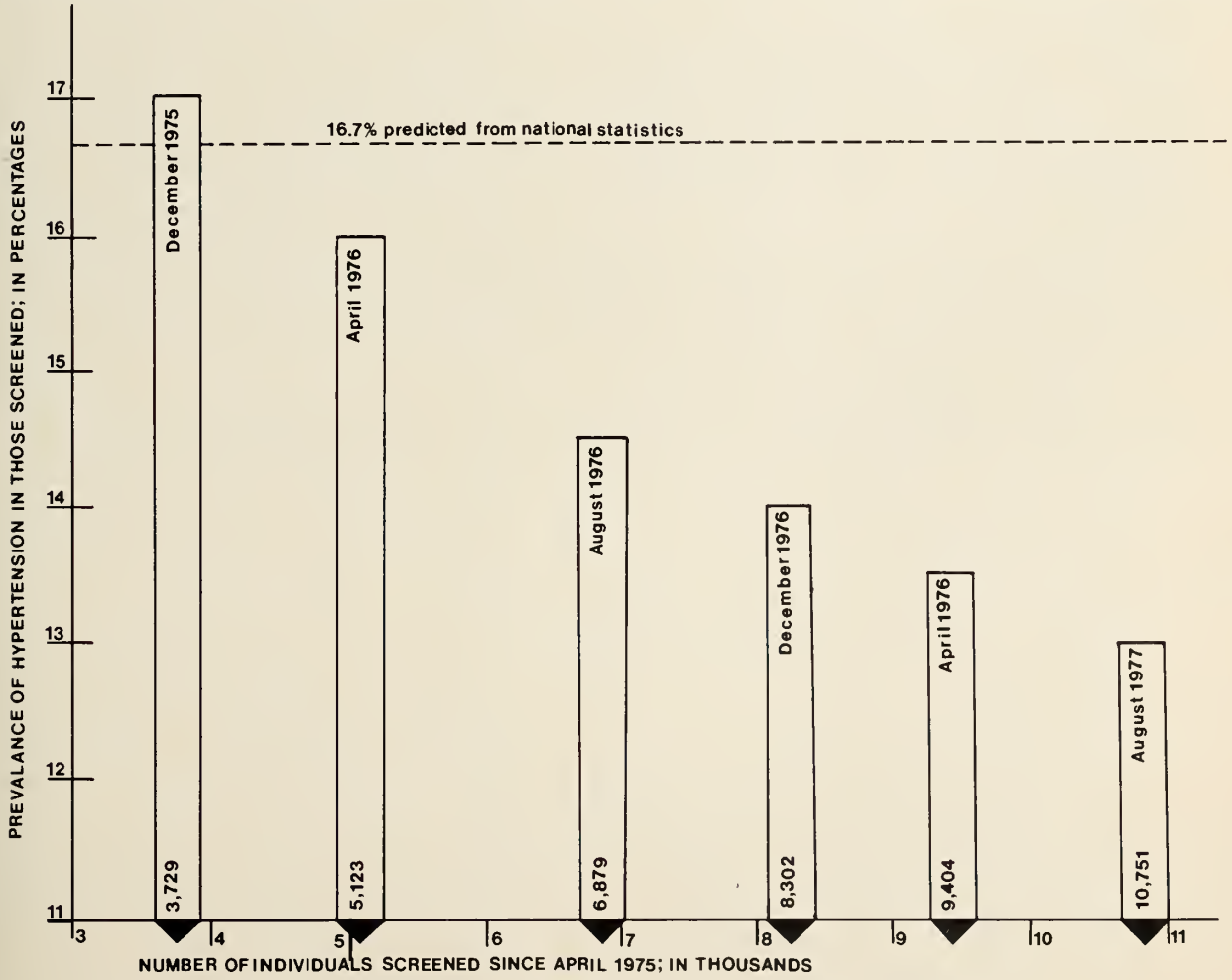

Figure 1.—Prevalence of hypertension in Whatcom County, Washington.

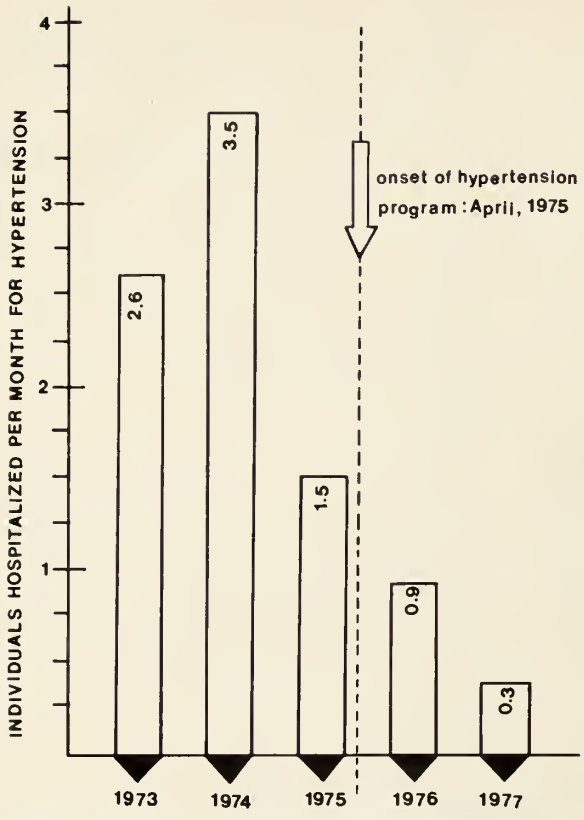

Figure 2.—Average monthly hospital admissions for hypertension to St. Luke's Hospital, Bellingham, Washington.

pressure above 95 mm of mercury are considered hypertensive. Those with normal blood pressures may return in 6 to 12 months for another free recording. In borderline cases, persons may return the following week and as often as necessary to clarify their status. Clearly abnormal results will elicit recommendations for a reasonably prompt check by personal physicians. Patients with severely elevated blood pressure, for example, diastolic pressures greater than 120 mm or 130 mm of mercury, find us assisting them to make an emergency visit to their doctors. Our screeners hand out educational booklets to hypertensive patients, so that they may better understand their disease.

All blood pressure readings are kept on permanent file in our clinic, and the patients are given wallet-sized cards with each of the recordings for their own use. They may give these to their physicians as additional data upon which to base therapeutic decisions.

We counted only persons seen, not numbers of blood pressure recordings. Many of the 10,751 persons have been checked several times in various stations. Duplicate records for the same person have been condensed and counted only once. Only the most recent blood pressure recording is counted in our statistics. People in whom hypertension was shown on earlier screenings and who since have regained normal blood pressure are now counted in the normotensive group. People who become hypertensive or in whom treated hypertension gets out of control are counted in the hypertensive group.

In October 1976 we were given a hypertension profile for our county based on national data from the CIBA Community Hypertension Evaluation Clinic (CHEC). The CHEC program had screened more than 1,000,000 Americans between 1973 and 1975.[8] The CHEC profile for Whatcom County predicted a 16.7 percent prevalence of hypertension, a figure quite close to ours in December 1975.

The declining prevalence of hypertension in our county is shown in Figure 1. The early screening data in December 1975 showed 17 percent of our population to be hypertensive. (Hypertension is defined as a diastolic pressure greater than 90 mm of mercury for those 40 years or younger, and greater than 95 mm of mercury for those over 40 years of age.) By August 1977 the percentage had fallen to 13 percent. If these figures are extrapolated to the total county population, 2,768 previously hypertensive patients are now normotensive.

The number of average monthly admissions to our community hospital before and during the antihypertension program is shown in Figure 2. Only patients admitted with the primary diagnosis of hypertension were counted. In the two years before the existence of an organized program, hospital admissions for hypertension were averaging approximately three per month. However, after April 1975 the hospital admission rate decreased to less than one patient per month.

A number of factors probably contributed to this decline. One was lack of enthusiasm locally for extensive laboratory and roentgenographic evaluation for secondary hypertension. Moreover, early diagnosis and treatment of hypertension prevent the need for hospital admission under crisis conditions. The shift from inpatient to outpatient therapy even for small numbers of patient is clearly a major saving. If such a phenomenon were to occur nationally, the saving could be huge.

Our program continues beyond its third year.

We expect the residuum of hypertension in Whatcom County to continue to decline. We expect heart failure, stroke and hypertensive renal failure to occur less often, and overall survival to increase. Although it is beyond our scope at present, we would welcome a study here to determine these factors.

Comment

Our efforts to control hypertension in a medium-sized community have resulted in a significant decline in the local prevalence of the disease. Emphasis on early identification and therapy avoids vastly more expensive inpatient evaluation and crisis care. The effectiveness of the physician (in private practice) has been increased by using paramedical and volunteer help. The nurse has a major role in decisions regarding entry into the health care process through her direction of a large screening program. The generosity of the volunteer screeners has been notable and stems from their belief in the value of preventive medicine.

We firmly believe that any cost-effective, substantial reduction of cardiovascular disease in our society will begin with a concentrated attack on hypertension. Our program has required a minimum of time and expense. Appreciation from the public and the motivation of the staff have made this endeavor a pleasant one. The ingredients for similar antihypertension programs can be found in most average communities and can be readily duplicated.

Summary

A combined community and private program in Whatcom County, Washington, to detect and treat hypertension is described. A hospital-based outpatient hypertension clinic coordinates screening at multiple sites; provides educational programs, treatment backup and dietetic instruction, and refers most patients who are found to be hypertensive to long-term therapy with their community physicians.

Between April 1975 and August 1977, a total of 10,751 randomly selected persons from the county population of 93,709 was screened. Early data in December 1975 showed a 17 percent prevalence of hypertension, a fairly typical figure for American communities. By April 1977 the prevalence of hypertension had dropped to 13 percent. Furthermore, local hospital admissions for hypertension had declined by 80 percent, resulting in a major cost saving. The ingredients for similar antihypertension programs could be found in most average communities and could be readily duplicated.

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Refer to: Werner SB: Sources of supply of selected immunobiologics (Information). West J Med 130:188-189, Feb 1979

Information

Sources of Supply of Selected Immunobiologics

S. BENSON WERNER, MD
Berkeley, California

WITHIN THE STATE OF CALIFORNIA, local health departments and physicians in private practice frequently call the California Department of Health Services, Infectious Disease Section, for information on where to obtain rarely used immunobiologics. In March 1976 a list of immunobiologics was prepared and distributed to all county health departments and physicians receiving our publication *California Morbidity*, to make this information more readily available.

The effort was well-received and it was subsequently suggested that we provide that information in THE WESTERN JOURNAL OF MEDICINE to reach a wider audience. The following represents the latest updating of that list but we must emphasize that we have not made an exhaustive effort to identify *all* producers of the materials listed (sources in the United States, especially in the West were preferentially listed, if any sources exist at all) and we stress that the California Department of Health Services in no way endorses the products or the specific manufacturers mentioned, nor are we recommending that any product be used. In fact, some of the agents listed are not recommended and there are immunobiologics such as skin test antigens that have become outmoded by the introduction of accurate serologic tests. Staff members of California's Infectious Disease Section are available for consultation on the advisability and use of these agents.

This list will undoubtedly become outdated; this writer would appreciate receiving reports of corrections or additions as they become known, so that the list can be revised and reissued periodically.

SKIN TEST ANTIGENS

Brucellergen (brucellosis*)
Not available.

Cat scratch fever
Unlicensed antigen, available only by special arrangement with S. S. Kalter, PhD, Southwest Foundation for Research and Education, P.O. Box 2296, San Antonio, TX 76902, (512) 674-1410

Coccidioidin*
Cutter Laboratories, 4th and Parker Streets, Berkeley, CA 94710, (415) 841-0123; Berkeley Biologicals, 1831 Second St., Berkeley, CA 94710, (415) 843-6846 (for Spherulin); Iatric Corp., 2330 South Industrial Park Drive, Tempe, AZ 85282, (602) 966-7248

Diphtheria toxin (Schick Test)
Massachusetts Public Health Biologic Laboratories, 375 South Street, Boston, MA 02130, (617) 522-3700

Echinococcin* (Casoni)
Tropical Disease Lab., 1617 HSW, University of California Medical Center, San Francisco, CA 94143, (415) 666-2166 or 666-2167

Filariasis*
Not available. (Testing done *at* Department of International Health, University of California Medical Center, San Francisco, with antigen prepared by Center for Disease Control, [415] 666-1872)

Histoplasmin*
Parke-Davis, Joseph Campau at the River, Detroit, MI 48232, (313) 567-3300

Kveim (Sarcoid)
Dr. Gerard Favez, Clinique Cevey-Sylvana, 1066 Epalinges/Lausanne, Switzerland

Leishmaniasis*
Not available. (Testing done *at* Department of International Health, University of California Medical Center, San Francisco, with antigen from Wellcome Laboratories, England, [415] 666-1872)

Lepromin (leprosy)
Not available.

Lymphogranuloma venereum (Frei test)*
Not available.

Mumps*
Eli Lilly and Co., Indianapolis, IN 46206, (317) 636-2211

Scarlet fever toxin (Dick test)
Not available.

Schistosomiasis*
Not available. (Testing done *at* Department of International Health, University of California Medical Center, San Francisco, with antigen from World Health Organization, [415] 666-1872)

Toxoplasmosis*
Not available.

Trichinella*
Not available.

Tularemia*
Available to MD's from Immunobiologics, Center for Disease Control (CDC), Atlanta, GA 30333, (404) 329-3356, as an Investigational New Drug

*Serologic tests are also available (through local or state health department laboratories)

From the Infectious Disease Section, California Department of Health Services, Berkeley.

Submitted, revised, January 10, 1979.

Reprint requests to: S. Benson Werner, MD, Infectious Disease Section, California Department of Health Services, 2151 Berkeley Way, Berkeley, CA 94704.

VACCINES

Anthrax
Prepared by Michigan Department of Public Health Laboratories, Lansing, MI 48909, (517) 373-1290, and available to MD's from Immunobiologics, CDC (404) 329-3356

Meningococcal monovalent A, monovalent C, or bivalent AC
Prepared by Connaught Laboratories, Inc., Swiftwater, PA 18370 and distributed by Elkins-Sinn, Inc., 6711 E. Washington Boulevard, Los Angeles, CA 90040, (213) 723-3681; and Merck, Sharpe, and Dohme, West Point, PA 19486, (215) 699-5311. Release of monovalent or bivalent meningococcal vaccines requires approval from Bureau of Biologics, Food and Drug Administration, when use is for epidemic control.

Plague
Cutter Laboratories, 4th and Parker Streets, Berkeley, CA 94710, (415) 841-0123

Polio, inactivated (Salk)
Connaught Laboratories Limited, Ontario, Canada and distributed by Elkins-Sinn, Inc., 6711 E. Washington Boulevard, Los Angeles, CA 90040. (213) 723-3681

Rabies, duck embryo vaccine (DEV) origin
Eli Lilly and Co., Indianapolis, IN 46266, (317) 636-2211

Rabies, human diploid cell strain (HDCS) origin
Available from Center for Disease Control, (404) 329-3727 days, (404) 329-3644 nights, weekends and holidays, as an Investigational New Drug when (1) there is life-threatening reaction to duck embryo vaccine (DEV) or (2) DEV does not give adequate antibody titer. Wyeth Laboratories in Marietta, PA, will probably be licensed in 1979 or 1980 to produce and distribute HDCS commercially.

Rocky Mountain Spotted Fever
Not available.

Typhus
Lederle Laboratories, Pearl River, NY 10965, (914) 735-5000

ANTITOXINS AND IMMUNOGLOBULINS

Botulism antitoxin *(equine)* (Trivalent ABE)
Connaught Laboratories Limited, Ontario, Canada. Available from California Department of Health Services, Infectious Disease Section, by supply from Immunobiologics, CDC.

(Bivalent AB)
Not available.

Diphtheria antitoxin *(equine)*
Connaught Laboratories, Inc., Swiftwater, PA 18370 and distributed by Elkins-Sinn, Inc., 6711 E. Washington Boulevard Los Angeles, CA 90040, (213) 723-3681; Michigan Department of Public Health Laboratories, Lansing, MI 48909, (517) 373-1290; and Sclavo, Inc., 5 Mansard Court, Wayne, NJ 07470, (201) 696-8300 or (800) 526-5260

Gas gangrene, polyvalent
Not available.

Hepatitis B immune globulin (HBIG)
Abbott Laboratories, Diagnostics Div., Routes 137 and 43, Abbott Park, North Chicago, IL 60064, (800) 323-9100

Mumps immune globulin
Cutter Laboratories, 4th and Parker, Berkeley, CA 94710, (415) 841-0123

Rabies immune globulin (RIG) *(human origin)*
Cutter Laboratories, San Lorenzo, CA, (415) 276-8200, or Dallas, TX, (214) 661-5850

Rabies antiserum *(equine)*
Lederle Laboratories, Pearl River, NY; and Sclavo, Inc., 5 Mansard Court, Wayne, NJ 07470, (201) 696-8300. Available from many local pharmacies, county health departments.

Snake antivenin, *(equine) Crotalidae*, polyvalent
Wyeth Laboratories, Wasp and Biddle Streets, Marietta, PA 17547, (717) 426-1941

Snake antivenin, *(equine)* Coral
Wyeth Laboratories, Wasp and Biddle Streets, Marietta, PA 17547, (717) 426-1941

Spider antivenin, *(equine)* Black widow
Merck, Sharpe and Dohme, West Point, PA 19486, (215) 699-5311

Staphylococcal antitoxin
Not available.

Tetanus antitoxin *(equine)*
Sclavo, Inc., 5 Mansard Court, Wayne, NJ 07470, (201) 696-8300 or (800) 526-5260

Tetanus immune globulin
Cutter Laboratories, Berkeley; Wyeth Laboratories, Marietta, PA; Parke-Davis, Detroit, MI; and Hyland Division, Travenol Laboratories, Inc., 3300 Hyland Avenue, Costa Mesa, CA 92626, (714) 540-5000 or (800) 854-3235

Vaccinia immune globulin (VIG)
Center for Disease Control, Atlanta, GA 30333, (404) 329-3526 days and (404) 329-3644 nights, weekends and holidays

Varicella—Zoster immune globulin (VZIG)
Dr. John A. Zaia, Sidney Farber Cancer Institute, Boston, MA 02115, (617) 732-3121 as an Investigational New Drug

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

CLINICAL PHARMACOLOGY—Basic Principles in Therapeutics—Second Edition—Edited by Kenneth L. Melmon, MD, Professor of Medicine and Pharmacology, and Chief, Division of Cliinical Pharmacology; and Howard F. Morrelli, MD, Professor of Medicine and Pharmacology, and Vice Chairman (House Staff Affairs), Department of Medicine; University of California, San Francisco. Macmillan Publishing Co., Inc., 866 Third Avenue, New York City (10022), 1978, 1,146 pages, $25.00 (cloth); $19.95 (paperback).

This second edition of a textbook that seems destined to become a standard reference work testifies to the advantages of hindsight and "Phase IV" reevaluation, even in textbooks *about* drugs. The unit dealing with basic principles has been enlarged to include chapters on pharmacokinetics, psychologic factors, and the use of drugs in pregnancy and young children. Other important additions include chapters on alcohol and drug abuse as well as the treatment of poisoning. As a result of an apparent shift of emphasis from textbook to reference source, the case studies that constituted a separate unit in the first edition have been deleted.

Like all textbooks covering areas of great growth in new knowledge, *Clinical Pharmacology* has some obvious omissions, such as no mention of phencyclidine ("angel dust") among the drugs of abuse. Other topics are not discussed or cross-referenced in appropriate sections. For example, the use of demeclocycline in the treatment of inappropriate secretion of antidiuretic hormone (ADH) is given brief mention in the section on renal drugs but is not included in the section on ADH.

Considered as a whole, however, this textbook fills an important need of modern medicine, in providing a ready source of authoritative commentary on the clinical use of drugs.

DAVID G. JOHNSON, MD
Associate Professor of Internal Medicine and Pharmacology
University of Arizona Health Sciences Center
Tucson, Arizona

* * *

REVIEW OF MEDICAL PHARMACOLOGY—Sixth Edition—Frederick H. Meyers, MD, Professor of Pharmacology; Ernest Jawetz, MD, PhD, Professor of Microbiology and Medicine, and Alan Goldfien, MD, Professor of Medicine, Departments of Medicine and Obstetrics and Cardiovascular Research Institute, School of Medicine, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1978. 762 pages, $14.50.

This biennial edition is intended to be an up-to-date guide for pharmacology and therapeutics for both students and practitioners. It is well organized. The strongest sections are those on general principles, classic drugs, scientific approach to drug investigation, cancer chemotherapy, chemotherapeutic agents, mechanisms of action of antimicrobials (particularly inclusion of autolysins as one of the mechanisms of penicillin action), combination antimicrobial therapy and prophylactic therapy. Mechanisms are generally explained well and illustrated well. The charts, tables and structural formulas are very useful. The section on drug abuse is good perspective but appears sometimes to be historical in this rapidly changing area. The vasculitis syndrome seen with methamphetamines or methylphenidate with hepatitis B should be added.

Generally the perspective on new drugs or uses is cautious. Thus the section on propanolol is excellent but the widely used dopamine deserves more space. The combination of thiazide therapy with prazosin is mentioned but the rather common use with furosemide is omitted. Reduction of after load by sodium nitroprusside is given short shrift considering the wide clinical acceptance; the same is true for the long-acting nitrates. Most clinicians would favor nitroprusside for immediate relief of life-threatening hypertension rather than the cited diazoxide.

The introduction of serum assays as adjuncts in monitoring aminophylline and digoxin toxicity appears to have had little effect. Few clinicians would agree with the implication that digitalis leaf could be the preparation of choice if one became familiar with it.

The chemotherapy section is generally current except for the following: vancomycin has wide applicability in dialysis patients and in patients with methicillin-resistant staphylococcal infections. Likewise the current preparation of vancomycin is less toxic than indicated and probably is free of nephrotoxicity. Kanamycin listed on Table 48-1 would have little applicability for therapy against cited organisms in centers other than certain pediatric units; amikacin seems to have been given less attention than deserved and a more appropriate reference source would be *American Journal of Medicine* 62: June 1977. The polymyxins are not "becoming more important" despite *in vitro* test results; they are only rarely used and are generally ineffective in serious infections.

Although emphasis has been placed on square meters for establishing proper doses and the need to monitor renal function and assays of drugs, a guideline for estimated creatinine clearances should be included for the aminoglycosides. Atypical mycobacteria cannot be lumped together for comments on therapy. The cefazolin dosages advocated (0.5 to 1.0 grams every four hours) are high except for the most serious infections. The widely used carbenicillin needs to have hypokalemic alkalosis stressed as a side effect. Cefamandole is a cephalosporin and not a cephamycin as stated. Legionnaires' disease should be added as an indication for erythromycin therapy. The recommendations by others for initial combined therapy for suspected Haemophilus influenzae meningitis with ampicillin and chloramphenicol has been omitted. Use of hepatitis B immune globulin deserves more discussion. Only some of these are related to recent developments.

In general, the sources and references are appropriate. The cautious approach of the authors makes this book suitable for students preparing for board examinations but the clinician will need other sources for guidelines in current therapeutics.

RICHARD D. MEYER, MD
Assistant Chief, Infectious Disease Section
VA Wadsworth Medical Center
Assistant Professor, UCLA School of Medicine
Los Angeles

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Each tablet contains aspirin, [illegible] and caffeine 32 mg plus codeine phosphate in one of the following strengths: #4—60 mg (gr 1) #3—30 mg (gr ½) #2—15 mg (gr ¼) and #1—7.5 mg (gr ⅛)
(Warning—may be habit forming)

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Average weight loss of 2.15 lbs per week compared in clinical studies against a placebo.

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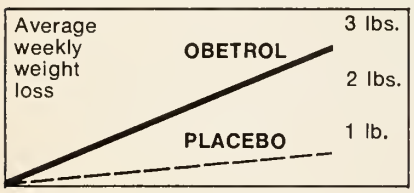
72 CASES 4 WEEKS' RESULTS



Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

Availability: Supplied in bottles of 100; 500 and 1,000 tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

January 1973

Comprehensive informational brochure available upon written request. Prescribe Obetrol for appetite control.

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Ortho announces

an important in the treatment of

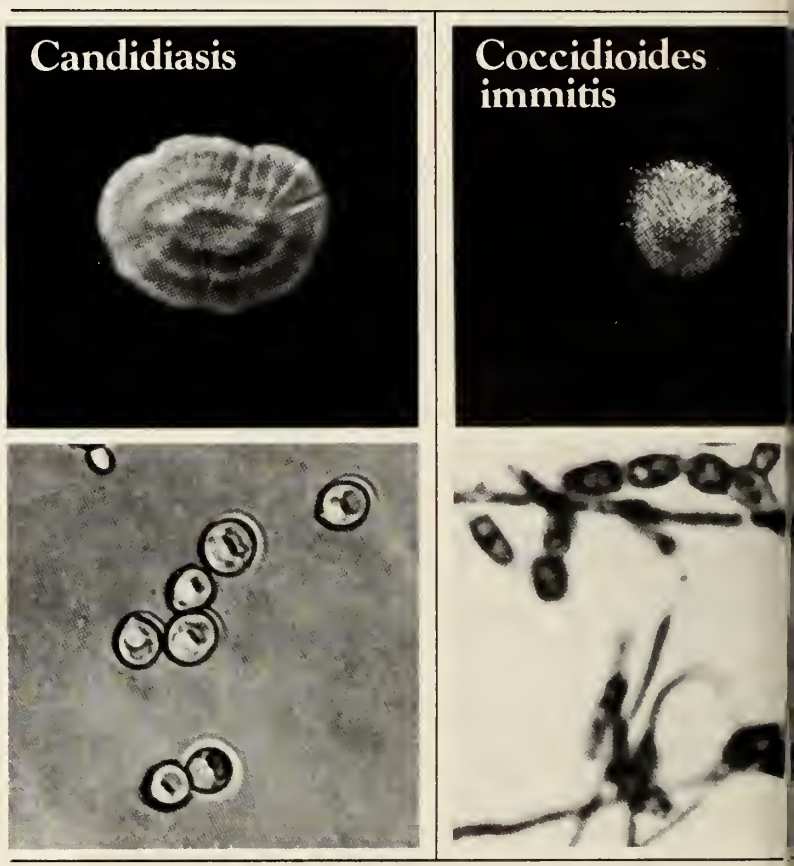
Efficacy of MONISTAT i.v. therapy...

highly favorable rates of recovery or clinical improvement

- effective against systemic candidiasis
  - chronic mucocutaneous candidiasis
  - coccidioidomycosis
  - cryptococcosis
  - paracoccidioidomycosis
- in patients who did not respond to amphotericin B therapy
- in immunologically-compromised patients with severe infections

rapid onset of clinical improvement
In most patients who responded, improvement was observed within 1-3 weeks of MONISTAT i.v. therapy; however, prolonged treatment courses may be necessary to prevent relapse.

no development of fungal resistance during therapy reported
In vitro resistance of clinical isolates has not been observed during clinical trials.



Photos courtesy of Dubos, J. R., Bacterial and Mycotic Infections of Man, J. B. Lippincott Company, 1968 and Burrows, W., Textbook of Microbiology, W. B. Saunders Company, 19th edition.

and the side effect profile

no nephrotoxicity or other permanent adverse effects in clinical studies

- even in prolonged therapy
- even in patients with renal disease

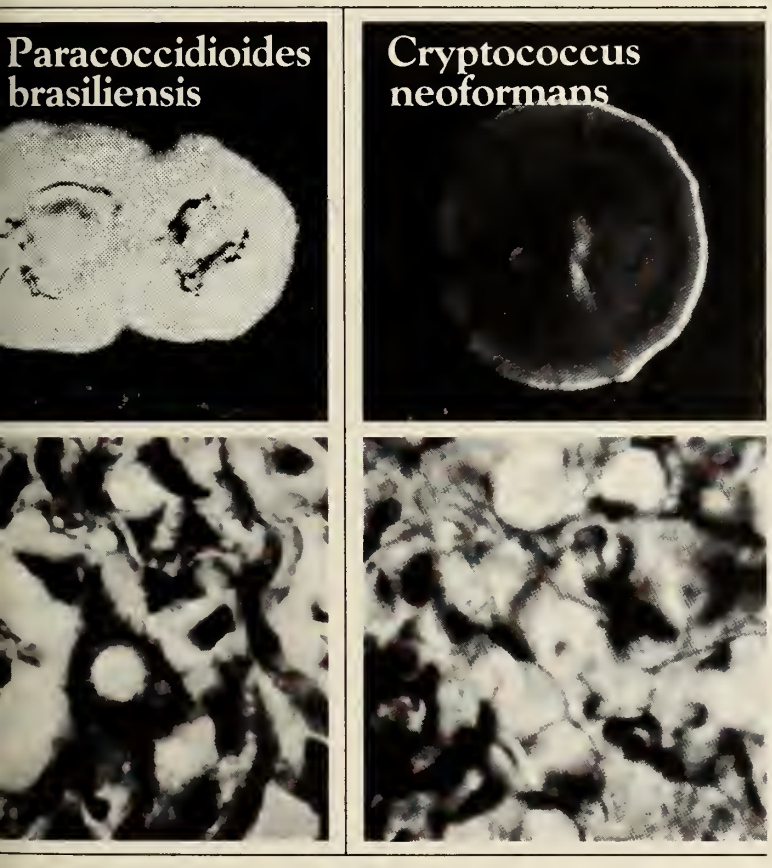
extensively evaluated
During clinical trials in over 400 patients, no permanent adverse reactions were reported.

Adverse reactions
MONISTAT i.v. should not be administered undiluted. Rapid injection of the undiluted solution may produce transient tachycardia or arrhythmia.

Adverse reactions include phlebitis, pruritus, rash, nausea, vomiting, febrile reactions, drowsiness, diarrhea, anorexia and flushes. Transient hematologic changes have occurred; therefore, the patient should be closely monitored.

© OPC 1978

advancement systemic mycoses



generally well tolerated by severely debilitated patients

- cancer patients
- patients receiving immunosuppressive drugs
- patients with serious underlying conditions such as renal insufficiency or diabetes mellitus

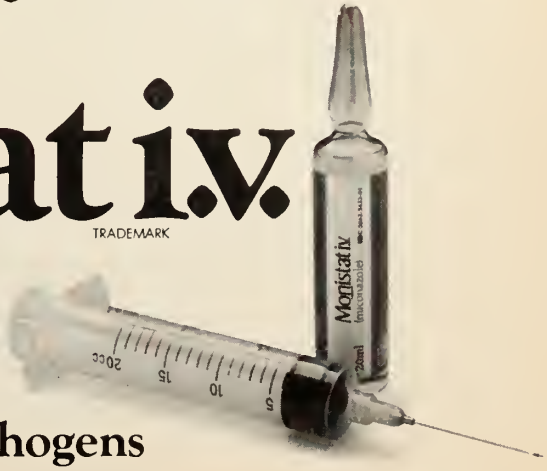
for more information

Because of the uniqueness of new MONISTAT i.v. only some of the highlights can be presented in this advertisement. For more information, i.e., product monograph, dosage schedules, etc., please fill out the coupon on the next page and mail to Ortho Pharmaceutical Corporation.

Please turn page for Prescribing Information

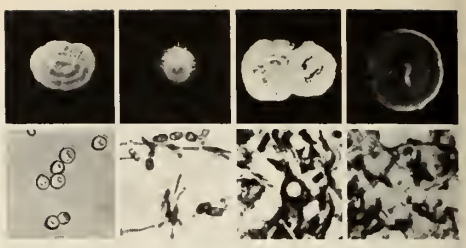
Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

new Monistat i.v.
TRADEMARK
(miconazole)



broad-spectrum activity against major systemic fungal pathogens

in systemic fungal infections...



new Monistat i.v. (miconazole)

TRADEMARK

a broad-spectrum systemic antifungal agent

DESCRIPTION: MONISTAT i.v. (miconazole) 1-{2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl) methoxyl ethyl} 1 H-imidazole is a synthetic antifungal supplied as a sterile solution for intravenous infusion. Each ml of this solution contains 10 mg of miconazole with 0.115 ml PEG 40 castor oil, 1.0 mg lactic acid USP, 0.5 mg methylparaben USP, 0.05 mg propylparaben USP in water for injection. Miconazole i.v. is a clear, colorless to slightly yellow solution having a pH of 3.7 to 5.7.

CLINICAL PHARMACOLOGY: MONISTAT i.v. is rapidly metabolized in the liver and about 14% to 22% of the administered dose is excreted in the urine, mainly as inactive metabolites. The pharmacokinetic profile fits a three-compartment open model with the following biologic half-life: 0.4, 2.1, and 24.1 hours for each phase respectively. The pharmacokinetic profile of MONISTAT i.v. is unaltered in patients with renal insufficiency, including those patients on hemodialysis. The in vitro antifungal activity of MONISTAT i.v. is very broad. Clinical efficacy has been demonstrated in patients with the following species of fungi: *Coccidioides immitis, Candida albicans, Cryptococcus neoformans, and Paracoccidioides brasiliensis.*

Recommended doses of MONISTAT i.v. produce serum concentrations of drug which exceed the in-vitro MIC values for the fungal species noted above. Doses above 9 mg/kg of MONISTAT i.v. produce peak blood levels above 1 μg/ml in most cases. The drug penetrates into joints.

INDICATIONS: MONISTAT i.v. is indicated for the treatment of the following severe systemic fungal infections: coccidioidomycosis, candidiasis, cryptococcosis, paracoccidioidomycosis, and for the treatment of chronic mucocutaneous candidiasis. However, in the treatment of fungal meningitis and urinary bladder infections an intravenous infusion alone is inadequate. It must be supplemented with intrathecal administration and bladder irrigation. Appropriate diagnostic procedures should be followed and MICs should be determined

MONISTAT i.v. should not be used to treat common trivial forms of fungal diseases.

CONTRAINDICATIONS: MONISTAT i.v. is contraindicated in those patients who have shown hypersensitivity to it.

WARNINGS: Rapid injection of undiluted MONISTAT i.v., may produce transient tachycardia or arrhythmia.

PRECAUTIONS: Before a treatment course of MONISTAT i.v. is started, the physician should make sure that the patient is not hypersensitive to the drug product. MONISTAT i.v. should be given by intravenous infusion. The treatment should be started under stringent conditions of hospitalization but subsequently may be given to suitable patients under ambulatory conditions with close clinical monitoring. It is recommended that an initial dose of 200 mg be given with the physician in attendance. It is also recommended that clinical laboratory monitoring including hemoglobin, hematocrit, electrolytes and lipids be performed.

It should be borne in mind that systemic fungal mycoses may be complications of chronic underlying conditions which in themselves may require appropriate measures.

Pregnancy: Reproductive studies with MONISTAT i.v. in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus. There are no data, however, on the use of the drug in pregnant women.

Children: Since the safety of miconazole i.v. in children under one year of age has not been extensively studied, its benefits in this age group must be weighed against the possible risks involved.

ADVERSE REACTIONS: Adverse reactions which have been observed with MONISTAT i.v. therapy include phlebitis, pruritus, rash, nausea, vomiting, febrile reactions, drowsiness, diarrhea, anorexia and flushes. In the U.S. studies, 29% of 209 patients studied had phlebitis, 21% pruritus, 18% nausea, 10% fever and chills, 9% rash, and 7% emesis. Transient decreases in hematocrit and serum sodium values have been observed following infusion of MONISTAT i.v. Thrombocytopenia has also been reported. No serious renal or hepatic toxicity has been reported. If pruritus and skin rashes are severe, discontinuation of treatment may be necessary. Nausea and vomiting can be mitigated with antihistaminic or antiemetic drugs given prior to MONISTAT i.v. infusion, or by reducing the dose, slowing the rate of infusion, or avoiding administration at mealtime.

Aggregation of erythrocytes or rouleau formation on blood smears has been reported. Hyperlipemia has occurred in patients and is reported to be due to the vehicle, Cremophor EL (PEG 40 castor oil).

DRUG INTERACTIONS: Drugs containing cremophor-type vehicles are known to cause electrophoretic abnormalities of the lipoprotein. These effects are reversible upon discontinuation of treatment but are usually not an indication that treatment should be discontinued.

Interaction with the coumarin drugs resulting in an enhancement of the anticoagulant effect has also been reported. In cases of simultaneous treatment with MONISTAT i.v. and coumarin drugs, the anticoagulant effect should be carefully titrated since reductions of the anticoagulant doses may be indicated

DOSAGE AND ADMINISTRATION

DOSAGE

Adults. The doses may vary with the diagnosis and with the infective agent, from 200 to 1200 mg per infusion. The following daily doses, which may be divided over 3 infusions, are recommended:

Organism	Dosage Range*	Duration of Successful Therapy (weeks)
Coccidioidomycosis:	1800 to 3600 mg per day	3 to > 20
Cryptococcosis:	1200 to 2400 mg per day	3 to > 12
Candidiasis:	600 to 1800 mg per day	1 to > 20
Paracoccidioidomycosis:	200 to 1200 mg per day	2 to > 16

*May be divided over 3 infusions.

Repeated courses may be necessitated by relapse or reinfection.

Children: A total daily dose of about 20 to 40 mg/kg is generally adequate. However, a dose of 15 mg/kg body weight per infusion should not be exceeded.

ADMINISTRATION: MONISTAT i.v. should be diluted in at least 200 ml of fluid. The diluent of choice is 0.9% sodium chloride or alternatively Dextrose 5% injectable solution. The intravenous infusion should be given over a period of 30 to 60 minutes.

Generally, treatment should be continued until all clinical and laboratory tests no longer indicate that active fungal infection is present. Inadequate periods of treatment may yield poor response and lead to early recurrence of clinical symptoms. The dosing intervals and sites and the duration of treatment vary from patient to patient and depend on the causative organism

OTHER MODES OF ADMINISTRATION: Intrathecal. Administration of the undiluted injectable solution of MONISTAT i.v. by the various intrathecal routes (20 mg per dose) is indicated as an adjunct to intravenous treatment in fungal meningitis. Succeeding intrathecal injections may be alternated between lumbar, cervical, and cisternal punctures every 3 to 7 days. Bladder instillation of 200 mg of diluted solution is indicated in the treatment of mycoses of the urinary bladder.

HOW SUPPLIED: MONISTAT i.v. is supplied in 20 ml ampoules.

MONISTAT i.v. (miconazole) is an original product of Janssen Pharmaceutica N.V., Belgium, and co-developed by Ortho Pharmaceutical Corporation.

WJ2/79

Ortho Pharmaceutical Corporation
c/o 733 Summer Street
Stamford, CT 06901

Please send me more information on the new broad-spectrum, systemic antifungal agent...MONISTAT i.v. (miconazole).

_____ M.D.

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October 1978

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

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A reuseable pocket sized, alcohol tester.

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a simple, inexpensive way to quickly determine blood alcohol levels.

SAMPLES

breath easily and quickly gives a blood alcohol reading.

ELIMINATES

the expense and delay of a blood analysis, or the necessity of a breath tester using costly chemicals and other paraphernalia.

ACTUAL SIZE

- Can be used every 20 seconds if no alcohol is encountered in a subject, every 15 minutes where a positive reading has been registered.
- Reads only alcohol—does not react to breath acetone.
- Is simple to operate, ruggedly built, and accurate. (± 01% BAL).
- Mouthpieces are only 7¢ each.
- Is good for 3000 tests or 14 months, whichever comes first, and can be rebuilt for $75.00.
- Uses any commercially available standard for calibration, and needs no external power supply.
- Is capable of processing a blood sample for BAL result.

The Alco-Sensor II is proving useful in Alcohol Rehabilitation Facilities, Emergency Rooms, Industrial Safety Programs and in clinics around the world. Price $290.00 includes (Alco-Sensor II, standard, Manual and 25 mouthpieces.)

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

THE AMERICAN BIOMEDICAL NETWORK—Health Care Systems in America: Present and Future—Proceedings of the Aspen Interdisciplinary Symposium on the USA Health Care Systems, Oct 1976: Edited by Stacey B. Day, MD, PhD, DSc; Robert V. Cuddihy, BS, MBA, and H. Hugh Fudenberg, MD. Scripta Medica & Technica, 71 Valley Street, South Orange, NJ (07079), 1977. 334 pages, price not given (Paperback).

ATLAS OF THE ULTRASTRUCTURE OF HUMAN BREAST DISEASES—Ali Ahmed, MD(Manch), Senior Lecturer in Pathology, University of Manchester; Foreword by A. Colin P. Campbell, MB, ChB, MSc, FRCP(Edin), FRCPath, Emeritus Professor of Pathology, University of Manchester. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 182 pages, illustrated, $45.00.

BASIC SCIENCE OF NUCLEAR MEDICINE—Roy P. Parker, PhD, FInstP, Senior Lecturer in Medical Physics, Institute of Cancer Research, Royal Marsden Hospital, London; Peter H. S. Smith, BA, DPhil, Principal Physicist to the Clwyd and Gwynedd Health Authorities; Formerly Senior Physicist, Royal Marsden Hospital, London; David M. Taylor, PhD, DSc, FRIC, Senior Lecturer and Head of the Radiopharmacology Department, Institute of Cancer Research, Royal Marsden Hospital, London. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 374 pages, $19.50.

BASIC SURGICAL TECHNIQUES—Second Edition—R. M. Kirk, MS, FRCS, Consultant Surgeon, Royal Free Hospital, London. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 168 pages, $6.50.

BECOME AN EX-SMOKER—Brian G. Danaher, Post-doctoral fellow in the Stanford University School of Medicine's Heart Disease Prevention Program; and Edward Lichtenstein, Professor of Psychology, Clinical Program, University of Oregon—In THE SELF-MANAGEMENT PSYCHOLOGY SERIES: Carl E. Thoresen, PhD, General Editor, Stanford University. Prentice-Hall, Inc. Publishers, Englewood Cliffs, NJ (07632), 1978. 226 pages, $10.95 (Cloth); $4.95 (Paperback).

BETTER HEALTH THROUGH PREVENTIVE DENTISTRY AND NUTRITION—Monroe L. Billingslea, DDS, in private practice, Los Angeles. Brent House Publishers, 8500 S. Figueroa St., Suite No. 3, Los Angeles (90003), 1978. 147 pages, $8.95.

BIOLOGY OF BRAIN TUMORS: UICC Technical Report Series Volume 30—A series of Workshops on the Biology of Human Cancer Report No. 5—Edited by O. D. Laerum; D. D. Bigner and M. F. Rajewsky. International Union Against Cancer, 1978. 209 pages, copies are available for Swiss Francs, 15.00 per copy + postage and packaging from: The Managing Editor, International Union Against Cancer, 3 rue de Conseil-Général, CH -1205 Geneva, Switzerland.

THE CASTRATED FAMILY—Harold M. Voth, MD, Senior Psychiatrist and Psychoanalyst, Menninger Foundation, Topeka, Kansas. Sheed Andrews and McMeel, Inc., Kansas City, KS (6700 Squibb Road, Shawnee Mission, KS 66202), 1977. 239 pages, $9.95.

CLINICAL PHARMACOLOGY OF PSYCHOTHERAPEUTIC DRUGS—Leo E. Hollister, MD, Professor of Medicine and Psychiatry, Stanford University School of Medicine; Medical Investigator, Veterans Administration Hospital, Palo Alto, CA—Volume 1 in MONOGRAPHS IN CLINICAL PHARMACOLOGY—General Editor: Daniel L. Azarnoff, MD, Professor of Medicine and Pharmacology, University of Kansas. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 239 pages, $19.50.

CORONARY HEART DISEASE IN YOUNG WOMEN—Edited by M. F. Oliver, MD, FRCP, FRCPE, FFCM, FACC(Hon), Professor, Departments of Medicine and Cardiology, The Royal Infirmary, Edinburgh. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 262 pages, $23.50.

DIVERTICULAR DISEASE OF THE COLON—A New Solution to One of the Great Deficiency Diseases of Western Civilization—Neil S. Painter, MS(London), FRCS(England), FACS, D OBST, RCOG, Senior Surgeon, The Manor House Hospital, London; Hunterian Professor, Royal College of Surgeons of England, 1963. Keats Publishing, Inc., P.O. Box 876, New Canaan, CT (06840), 1975. 305 pages, $5.95 (Paperback).

DOUBLE BIND: The Foundation of the Communicational Approach to the Family—Edited by Carlos E. Sluzki, MD, Adjunct Associate Professor, Department of Psychiatry; Director, Behavioral Sciences, Family Practice Residency Program, University of California, San Francisco; and Donald C. Ransom, PhD, Assistant Professor (in Residence), Division of Ambula-

tory and Community Medicine, University of California, San Francisco; Behavioral Science Coordinator, Family Practice Residency Program, Sonoma Community Hospital, Santa Rosa, California. Grune & Stratton, Inc., West Coast Office: Harcourt Brace Jovanovich Bldg., 1001 Polk St., San Francisco, CA (94109), 1976. 359 pages, $19.75.

ELECTROMYOGRAPHY IN CLINICAL PRACTICE—Michael J. Aminoff, BSc, MD, MRCP, Associate Professor of Neurology, University of California, San Francisco. Addison-Wesley Publishing Company, Inc., Health Sciences Division, 2727 Sand Hill Road, Menlo Park, CA (94025), 1978. 216 pages, $24.00.

FAREWELL TO WELFARE—William S. Hendricks, MD. B. K. Ducky Enterprises, 8836 S. Vermont Avenue No. 2, Los Angeles (90044), 1978. 108 pages, $7.95 (Paperback).

FEMALE SEXUALITY FOLLOWING SPINAL CORD INJURY—Elle Friedman Becker. Accent Special Publications, Cheever Publishing, Inc., P.O. Box 700, Bloomington, IL (61701), 1978. 273 pages, spiral bound, $10,95. Shipped postage paid; Illinois residents add 5 percent sales tax from Ms. Elle Friedman Becker, 1571 Alvarado Ave., No. 1, Walnut Creek, CA 94596.

FOR TEENAGERS ONLY—Change Your Habits to Change Your Shape—Joanne P. Ikeda, RD, Nutrition Education Specialist, University of California, Berkeley. Bull Publishing Company, P.O. Box 208, Palo Alto, CA (94302), 1978. 126 pages, $4.95 (Paperback).

HANDBOOK OF CANCER IMMUNOLOGY—Volume 2: Cellular Escape From Immune Destruction—Edited by Harold Waters, PhD, Smithsonian Scientific Information Exchange, Weshington, DC (At present, a Heelth Science Administrator, Division of Reseerch Grants, NIH). Garland STPM Press, Division of Garland Publishing, Inc., 545 Madison Ave., New York City (10022), 1978. 275 pages, $37.50 (Five-volume set: $165.00).

HANDBOOK OF CANCER IMMUNOLOGY—Volume 3: Immune Status in Cencer Treetment end Prognosis, Pert A—Edited by Harold Waters, PhD, Smithsonlan Sclentific Information Exchange, Washington, DC (At present, e Health Sclence Administrator, Division of Research Grants, NIH). Garlend STPM Press, Division of Garlend Publishing, Inc., 545 Madison Ave., New York Clty (10022), 1978. 434 peges, $37.50 (Five-volume set: $165.00).

HANDBOOK OF CANCER IMMUNOLOGY—Volume 4: Immune Status In Cencer Treetment and Prognosis, Pert B—Edited by Harold Weters, PhD, Smithsonian Scientific Information Exchange, Washington, DC (At present, a Health Science Administrator, Division of Research Grants, NIH). Garland STPM Press, Division of Garland Publishing, Inc., 545 Madison Ave., New York City (10022), 1978. 335 pages, $37.50 (Five-volume set: $165.00).

HANDBOOK OF SURGERY—Sixth Edition—Edited by Theodore R. Schrock, MD, Associate Professor of Surgery, University of California, San Francisco. Jones Medical Publications, 355 Los Cerros Drive, Greenbrae, CA (94904), 1978. 596 pages, $10.00 (Softbound).

LET THE PATIENT DECIDE—A Doctor's Advice to Older Persons—Louis Shattuck Baer, MD. The Westminster Press, Witherspoon Building, Philadelphia, PA (19107), 1978. 156 pages, $4.95 (Paperback).

THE MANAGEMENT OF MEDICAL PRACTICE—John McCormick, MHA, Administrative Services, Mayo Clinic, Rochester, Minnesota; Ronald Lee Rushing, CPA, MBA, Director of Fiscal Services, Kelsey-Seybold Clinic, Houston; and W. Grayburn Davis, MD, Executive Vice President, American Group Practice Association, Alexandria, Virginia. Ballinger Publishing Company, 17 Dunster Street, Harvard Square, Cambridge, MA (02138), 1978. 388 pages, $20.00.

THE POISONS AROUND US—Henry A. Schroeder, MD. Keats Publishing, Inc., P.O. Box 876, New Canaan, CT (06840), 1974. 140 pages, $4.95 (Paperback).

RESTORATION OF MOTOR FUNCTION IN THE STROKE PATIENT—A Physiotherapist's Approach—Margaret Johnstone, MCSP; Illustrated by Estrid Barton; Foreword by Professor Bernard Isaacs, MD, FRCP, Charles Heyward Professor of Geriatric Medicine, University of Birmingham. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th Street, New York City (10036), 1978. 186 peges, $8.95.

SMOKING AND HOW TO STOP—Monroe L. Billingslea, DDS, In private practice, Los Angeles. Brent House Publishers, 8500 S. Figueroe St., Suite No. 3, Los Angeles (90003), 1978. 110 pages, $8.95.

WHOLISTIC DIMENSIONS IN HEALING—A Resource Guide—Compiled end Edited by Leslie J. Kaslof, founder of the International Institute for Biological end Botanicel Research, and of the National Council on Wholistic Therapeutics and Medicine, Brooklyn, New York. Doubleday & Compeny, Inc., 245 Perk Avenue, New York City (10017), 1978. 294 pages, $7.95 (Peperbeck).

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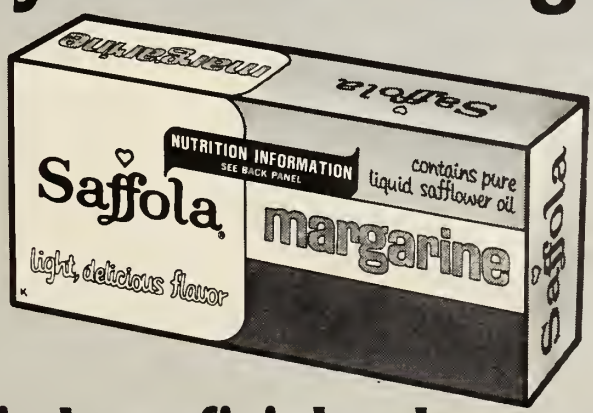

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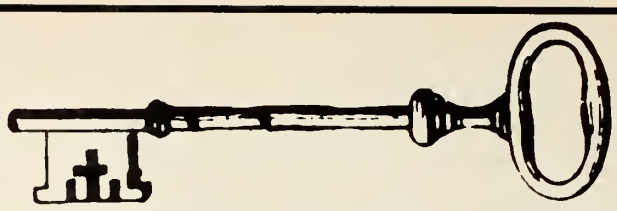

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ANESTHESIOLOGY

March 2-4—**Present and Future Clinical Use of Muscle Relaxants.** UCSF at Hyatt on Union Square, San Francisco. Friday-Sunday. 17 hrs. $175.

March 10-11—**Los Angeles County Society of Anesthesiologists—Postgraduate Assembly.** Hilton Hotel, Los Angeles. Saturday-Sunday. Contact: Virginia M. Connor, Exec. Sec., 184 N. Canon Dr., Beverly Hills 90210. (213) 275-4315.

March 18-23—**Anesthesiology 1979—5th Annual Winter Meeting.** Anesthesiology Educational Foundation and CSA at Mammoth Lakes. Sunday-Friday. Contact: Ronald L. Katz, MD, AEF, 3377 Colbert St., Los Angeles 90066.

April 20-22—**Newer Concepts and Older Practices in Obstetrical Anesthesia.** Fresno Community Hospital. Friday-Sunday. Contact: Joanne Ellis, Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

April 30-May 4—**California Society of Anesthesiologists—Hawaii Seminar.** Kauai Surf Hotel, Kauai. Monday-Friday. 20 hrs. Contact: CSA, Inc., 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

May 6-12—**16th Biennial Western Conference on Anesthesiology.** Sheraton Waikiki, Honolulu. One week. Contact: BWCA, 707-2525 Willow St., Vancouver, B.C., Canada V5Z 3N8.

May 31-June 4—**California Society of Anesthesiologists—Annuat Scientific Meeting.** Disneyland Hotel, Anaheim. Thursday-Monday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

CANCER

February 19-23—**Diagnosis and Management of the Complications of Cancer.** Scripps Clinic and Research Foundation at Holiday Inn at the Embarcadero, San Diego. Monday-Friday. 32 hrs. $280. Contact: Nomi Feldman, Box 705, La Jolla 92038. (714) 459-0511.

March 14-16—**Contemporary Gynecologic Oncology for the Practitioner.** UCSD at Vacation Village, San Diego. Wednesday-Friday.

March 16—**Annual Cancer Symposium.** California Hospital Medical Center, Los Angeles. Friday. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

March 17—**Cancer Viewpoints No. 8—Thyroid Cancer Diagnosis and Treatment.** American Cancer Society, Contra Costa Unit, at John Muir Hospital, Walnut Creek. Saturday. Contact: ACS, Contra Costa Unit, 1341 Newell Ave., Walnut Creek 94596. (415) 934-7640.

March 23-24—**Body Image, Self-Esteem and Sexuality in Cancer Patients—14th Annual San Francisco Cancer Symposium.** West Coast Cancer Foundation and St. Mary's Hospital and Medical Center at Hyatt on Union Square, San Francisco. Friday-Saturday. $100 before Dec. 1; $125 after. Contact: Jerome M. Vaeth, MD, WCCF, 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

April 4-6—**American Cancer Society National Conference—Urologic Cancer 1979.** Hilton Hotel, Los Angeles. Wednesday-Friday. 15½ hrs. Contact: Urologic Cancer Conference. 777 Third Ave., New York 10017. (212) 371-2900, ext. 239.

April 7—**San Joaquin County American Cancer Society Conference—2nd Annual.** ACS, San Joaquin-Calaveras Unit, and San Joaquin Hospital at San Joaquin Delta College, Stockton. Saturday. 7 hrs. $25. Contact: ACS, San Joaquin-Calaveras Unit, 1111 W. Robinhood Dr., Stockton 95207.

May 12—**Genital Urinary Cancer.** San Francisco Regional Cancer Foundation at Fireman's Fund Building, San Francisco. Saturday. 4 hrs. Contact: Norma Schlager, PhD, S.F. Regional Cancer Fnd., 14th and Lake, San Francisco 94118. (415) 221-2132.

June 1-2—**Oncology Symposium.** Area Health Education Center, UCSF, at Del Monte Hyatt, Monterey. Friday-Saturday. Contact: Remi Barron, Area Health Education Ctr., P.O. Box 1611, Salinas 93902. (408) 757-3616.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

EMERGENCY MEDICINE

February 26—**Oral and Maxillofacial Trauma.** Gen. Hos. Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at Gen. Hosp., Ventura. Monday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp. Ventura Co., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

March 19-23—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Bahia Hotel, San Diego. Monday-Friday. 40 hrs. $350.

March 22—**Venous Animal Injuries.** General Hospital Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at Gen. Hosp., Ventura. Thursday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

March 26-29—**American College of Emergency Physicians—Annual Symposium.** Del Monte Hyatt, Monterey. Monday-Thursday. 16 hrs. $235, members; $265, nonmembers. Contact: Registrar, ACEP, 3900 Capital City Blvd., Lansing, MI 48906. (517) 321-7913.

April 2-6—**Medical Management of EMS Systems.** UCSD at Hilton, San Diego. Monday-Friday. 36 hrs. $120.

April 16-20—**Postgraduate Institute for Emergency Physicians, Symposium IV.** UCSD at Hilton Hotel, San Diego. Monday-Friday.

April 21-28—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 29 hrs. $325.

April 30—**Polyneuropathies.** General Hospital Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at General Hospital, Ventura. Monday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

May 7-11—**Topics in Emergency Medicine.** UCSF at Sheraton, Fisherman's Wharf, San Francisco. Monday-Friday.

May 14-18—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Islandia Hyatt House, San Diego. Monday-Friday. 40 hrs. $350.

May 19—**Emergency Radiology.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7½ hrs. $50.

May 21—**Hand Injuries.** General Hospital Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at General Hospital, Ventura. Monday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

May 26-June 2—**Annual Symposium on Diagnosis and Management of Medical Emergencies.** West Hills Hospital at Royal Lahaina Hotel, Maui, Hawaii. One week. 30 hrs. Contact: Charlotte McGuire, Adm. Coordinator, Medical Staff, West Hills Hosp., 7300 Medical Center Dr., Canoga Park 91307. (213) 884-7060, ext. 200.

June 25-29—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

MEDICINE

February 15-16—**Pulmonary Function Evaluation: Clinical Application of New Techniques.** Memorial Hospital Medical Center, Long Beach. Thursday-Friday. 12 hrs. $150. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 17—**Viral and Viral-Like Lesions of the Liver.** Memorial Hospital Medical Center, Long Beach. Saturday. 8 hrs. $105. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 17—**Perspectives in Immune and Hypersensitivity Lung Disease—5th Annual Pulmonary Symposium.** USC and Inter-Community Hospital at Calif. Polytechnic Univ., Pomona. Saturday. 5 hrs. $25. Contact: Gregg Masters, Inter-Community Hosp., 303 N. 3rd Ave., Covina 91723. (213) 331-7331, ext. 2623.

February 21-23—**Daily Decisions in Lung Disease—Annual Postgraduate Course.** Calif. Thoracic Society at Red Lion Motor Inn, Sacramento. Wednesday-Friday. 16 hrs. $160, members; $180, nonmembers. Contact: Anna B. Roberts, Admin. Asst., CTS, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

February 24—**Workshop in Complex Arrhythmias.** PMC. Saturday.

February 24-25—**Dermatology, Allergy and Immunobiology.** UCLA. Saturday-Sunday. 14½ hrs. $150.

March 2—**What's New in Hematology.** PMC. Friday. 6 hrs. $95.

March 6-10—**Consultant's Course in Dermatology—7th Annual.** UCSF. Tuesday-Saturday.

March 7—**The Role of Radioimmunoassay in Clinical Medicine.** LA Soc. of Internal Medicine. Wednesday. 1 hr. Contact: Susan McNamara, LASIM, 8530 Wilshire Blvd., #313, Beverly Hills 90211. (213) 659-6750.

March 9-10—**Different Aspects of Genetic Red Blood Cell Defects.** UCSF. Friday-Saturday. 8 hrs. $50.

March 10-11—**Prevention of Crisis in the Patient with Chronic Respiratory Disease.** UCLA. Saturday-Sunday. 12 hrs. $95.

March 10-11—**Nuclear Medicine.** See Radiology and Pathology, March 10-11.

March 11-14—**Topics in Gastroenterology.** UCSF at Yosemite. Sunday-Wednesday.

March 14—**Ischemic Heart Disease.** LLU. Wednesday. 4 hrs.

March 17—**Clinical Aspects of Hypertension.** STAN. Saturday. 5 hrs. $30.

March 23-25—**Cardiac Symptoms, Arrhythmias and Holter Monitoring.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

March 26-28—**Occupational Skin Diseases.** UCSF at Golden Gateway Holiday Inn, San Francisco. Monday-Wednesday.

March 26-29—**American College of Physicians—60th Annual Session.** San Francisco. Monday-Thursday. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

March 26-April 6—**Intensive Review of Internal Medicine.** USC. Two weeks. 69 hrs. $325.

March 29-30—**International Symposium on the Larynx.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Friday.

March 29-30—**Cardiovascular Nuclear Medicine—Current Concepts and Their Clinical Applications.** Foundation for Cardiovascular Research and Peralta Hospital at Stanford Court Hotel, San Francisco. Thursday-Friday. 12 hrs. Contact: FCR, 201 N. El Molino, Suite 100, Pasadena 91101.

March 29-31—**Contemporary Management of Acute Myocardial Infarction by the Family Physician.** American College of Cardiology and American Academy of Family Physicians at Riviera Hotel, Palm Springs. Thursday-Saturday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 31—**Flexible Fiberoptic Bronchoscopy.** PMC. Saturday. 6 hrs. $325.

April 2-11—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 3-5—**American Laryngological, Rhinological and Otological Society—Annual Meeting.** See Surgery, April 3-5.

April 4—**Antimicrobial Therapy: The State of the Art.** L.A. Society of Internal Medicine. Wednesday. 1 hr. Contact:

Susan McNamara, LASIM, 8530 Wilshire Blvd., No. 313, Beverly Hills 90211. (213) 659-6750.

April 4-June 13—**Rheumatology for the Practicing Physician.** UCLA at Wadsworth VA Hospital Center, Los Angeles. Wednesday evenings. 20 hrs. $220.

April 11-13—**Review and Updating of the Immunology and Clinical Practice of Allergy—3rd Annual.** UCSD at Hilton Hotel, San Diego. Wednesday-Friday.

April 18—**Society of Nuclear Medicine, Southern California Chapter.** See Radiology and Pathology, April 18.

April 26-June 14—**Current Practical Cardiology—1979.** Daniel Freeman Hospital, Inglewood. Thursdays; 6:30-9:00 p.m. 16 hrs. $120. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., 333 N. Prairie, Inglewood 90301. (213) 674-7050, ext. 3427.

April 27—**Controversies in Cardiology.** American Heart Assn., Santa Clara County Chapter, at Le Baron Hotel, San Jose. Friday. 6 hrs. $30. Contact: Harriet M. Schutte, RN, PhD, AHA, Santa Clara Co. Chap., 3003 Moorpark Ave., San Jose 95128.

May 3-5—**Critical Care Cardiology.** PMC. Thursday-Saturday. 18 hrs.

May 4-6—**Sierra Valley Nuclear Medicine Association.** See Radiology and Pathology, May 4-6.

May 4-6—**Coronary Disease, Exercise Testing and Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton Inn, San Diego. Friday-Sunday. 13 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

May 5—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

May 11-13—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Sunday. 15 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

May 12—**Controversies in Internal Medicine—3rd Annual Program.** San Jose Health Center at Marriott's Great America, Santa Clara. Saturday. 6 hrs. $40. Contact: Stanley Skillicorn, MD, Dir. of Med. Ed., San Jose Health Ctr., 675 E. Santa Clara, San Jose 95112. (408) 998-3212.

May 12-13—**Management of Thrombo-Embolic Disease in Clinical Practice.** UCLA. Saturday-Sunday. 14 hrs.

June 3-9—**Advances in Internal Medicine.** USCF at Hyatt on Union Square, San Francisco. One week.

June 9-10—**Practical Cardiology for the Primary Care Physician.** UCLA. Saturday-Sunday.

June 20-22—**Pediatric Gastroenterology.** See Pediatrics, June 20-22.

June 21-23—**Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. Contact: Mary Anne McInerny, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 27-29—**Hepatobiliary Disease in Clinical Practice.** PMC at Holiday Inn on Union Square, San Francisco. Wednesday-Friday. 15 hrs. $180.

July 13-15—**Cardiac Symptoms, Arrhythmias and Holter Monitoring.** International Medical Education Corp. at Hyatt, Anaheim. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

July 19-20—**New Approaches to Immunosuppression.** PMC at Fairmont Hotel, San Francisco. Thursday-Friday. 12 hrs. $100.

July 23-24—**Microcirculatory Approach to Current Medical and Surgical Problems.** Microcirculatory Society and American Heart Assn., Greater Los Angeles Affiliate, at Hilton, San Diego. Monday-Tuesday. 14 hrs. $175, before April 1; $200, thereafter. Contact: Nomi Feldman, Conf. Coordinator, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

July 27-29—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Sunday. 15 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

July 30-August 3—**Endocrinology and Metabolism.** UCSF at Hyatt Regency, San Francisco. Monday-Friday.

August 4—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

OBSTETRICS AND GYNECOLOGY

February 21-23—**New Perspectives and Update in Perinatal Medicine.** USC at Hyatt Regency, Los Angeles. Wednesday-Friday. 22 hrs. $150.

March 8-9—**Practical Options in Perinatal Health Care.** UCD at Hyatt Lake Tahoe. Thursday-Friday. 8½ hrs. $100.

March 14-16—**Contemporary Gynecologic Oncology for the Practitioner.** See Cancer, March 14-16.

March 14-16—**Basic and Advanced Gyn Urology.** Women's Hospital of Long Beach, Memorial Hospital and Medical Center of Long Beach, UCI at Inn at the Park, Anaheim. Wednesday-Friday. 20 hrs. $300. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801.

April 15-21—**Current Dialogues in Obstetrics and Gynecology.** Memorial Hospital Medical Center of Long Beach and Women's Hospital of Long Beach at Kauai Surf, Kalapaki Beach, Hawaii. One week. 22 hrs. $300. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 9—**Hormones and Hormone Therapy.** LLU. Wednesday. 4 hrs.

May 21-23—**Recent Advances in Obstetrics and Gynecology.** UCSD at Vacation Village, San Diego. Monday-Wednesday.

PEDIATRICS

February 22-24—**Update on Pediatric Hematology—Annual Winter Meeting.** Children's Hospital Medical Center, Oakland, at Sahara Hotel, Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes, Med. Staff Office, CHMC, 51st and Grove Sts., Oakland 94609.

March 9-10—**Different Aspects of Genetic Red Blood Cell Defects.** See Medicine, March 9-10.

March 15-18—**Clinical Pediatrics—Combined Southern California Pediatric Postgraduate Meeting.** American Academy of Pediatrics, Calif. Chap. 2, at Riviera Hotel, Palm Springs. Thursday-Sunday. Contact: Eve Black, AAP, Calif. Chap. 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

April 6-7—**Practical Pediatric Endocrinology.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 9 hrs. $65.

May 7-11—**Pediatric Review—9th Annual.** USC. Monday-Friday.

May 9-11—**Care of the Sick Newborn.** Memorial Hospital Medical Center, Long Beach. Wednesday-Friday. 18 hrs. $125. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 10-12—**Annual Pediatric Course.** UCSF at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

May 12-19—**Pediatric Workshop.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week.

June 9—**Update of Pediatric Ophthalmology.** See Surgery, June 9.

June 20-22—**Pediatric Gastroenterology.** UCSF. Wednesday-Friday.

PSYCHIATRY

February 16-17—**Violence: What's Happening!—5th National Seminar.** Vista Hill Foundation at Hotel del Coronado, Coronado. Friday-Saturday. Contact: Keith S. Ditman, MD, Vista Hill Fnd., 7798 Starling Dr., San Diego 92123. (714) 278-6761.

February 22-25—**Sixth International Gender Dysphoria Symposium.** See Surgery, February 22-25.

February 23-24—**Psychiatric Aging.** UCD at Hyatt Lake Tahoe, Incline Village. Friday-Saturday.

February 27—**Continuing Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

March 23-25—**Clinical Management of Anxiety and Stress.** USC at Rancho Bernardo Inn, San Diego. Friday-Sunday. 13 hrs. $100.

March 27—**Continuing Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

April 7, 21—**The Family as Patient: Case Studies in Family Therapy.** UCLA. Two Saturdays.

April 24—**Continuing Medical Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

May 29—**Continuing Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

June 1-2—**Psychosocial Care of the Dying Patient.** UCSF. Friday-Saturday.

June 13—**Diagnosis and Office Management of Anxiety and Stress.** LLU. Wednesday. 4 hrs.

June 16-23—**Comparative Psychotherapies.** USC at Royal Lahaina, Maui, Hawaii. One week. 26¾ hrs. $300.

RADIOLOGY AND PATHOLOGY

February 28-March 2—**Anaerobic Bacteriology Methods.** Memorial Hospital Medical Center, Long Beach. Wednesday-Friday. 11½ hrs. Contact: Center for Health Education, Memorial Hospital Medical Center, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

March 3-9—**International Academy of Pathology, U.S.-Canadian Division—68th Annual Meeting.** Hilton Hotel, San Francisco. Monday-Friday. Contact: Leland D. Stoddard, MD, Dept. of Pathology, Medical College of Georgia, Augusta, GA 30901. (404) 724-2973.

March 9-11—**Gastrointestinal Radiology, Update '79.** San Diego Radiology Research and Education Foundation and ACR at San Diego. Friday-Sunday. 18 hrs. $200. Contact: Mary J. Ryals, Radiology, P.O. Box 2305, La Jolla 92038. (714) 453-7500, ext. 3711.

March 10-11—**Pediatric Radiology.** UCSF at Hyatt on Union Square, San Francisco. Saturday-Sunday.

March 10-11—**Nuclear Medicine.** UCSF at Hyatt on Union Square, San Francisco. Saturday-Sunday. 9 hrs. $125.

March 12-16—**Diagnostic Radiology.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday. 33 hrs. $300.

March 17-18—**Ultrasound.** UCSF at Hyatt on Union Square, San Francisco. Saturday-Sunday.

March 29-30—**Cardiovascular Nuclear Medicine.** See Medicine, March 29-30.

May 3-4—**Radiology Seminar—Clinical Problems.** UCSF. Thursday-Friday.

May 4-6—**Sierra Valley Nuclear Medicine Association—11th Annual Spring Symposium.** Northern Calif. Chapter, Society of Nuclear Medicine, at MGM Grand Hotel, Reno. Friday-Sunday. Contact: Cathy Suey, Nuclear Medicine, 4301 X St., Sacramento 95817.

April 7—**Imaging.** UCLA. Saturday.

April 18—**Society of Nuclear Medicine, Southern California Chapter—Annual Benedict Cassen Memorial Lecture Dinner Meeting.** L.A. Co. Med. Assn. Headquarters, Los Angeles. Wednesday. Contact: Jean Lynch, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

April 19-20—**Radiology Seminar—Clinical Problems.** UCSF. Thursday-Friday.

May 3-4—**Radiology Seminar—Clinical Problems.** UCSF. Thursday-Friday.

May 19—**Emergency Radiology.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7½ hrs. $50.

May 19-20—**Pathology of the Endocrine System.** UCLA at Long Beach Convention Center. Saturday-Sunday.

June 17-22—**Pathology of the Lung.** UCSD. Sunday-Friday.

July 28-August 4—**Medical Imaging.** American College of Medical Imaging at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

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SURGERY

February 15-16—**Corneal and External Disease.** UCSF. Thursday-Friday.

February 21-22—**American Orthopaedic Foot Society.** Civic Auditorium, San Francisco. Tuesday-Friday. 11 hrs. $40. Contact: R. A. Mann, MD, 5495 Fernhoff Rd., Oakland 94619. (415) 483-2500.

February 22-25—**Sixth International Gender Dysphoria Symposium.** UCSD at Hotel del Coronado, Coronado. One week.

February 23-24—**Phacoemulsification Surgery Course.** Jules Stein Eye Institute, Los Angeles. Friday-Saturday. 16 hrs. $300. Contact: Lu Hendricks, Jules Stein Eye Inst., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

February 24—**Enteral and Parenteral Nutrition: Update.** Santa Clara Co. Surgical Soc., Quad-Counties Pharm. Assn. and Abbott Labs at Rickey's Hyatt House, Palo Alto. Saturday. 7 hrs. $20. Contact for information: John F. Ryan, MD, (408) 275-6500 or Bruce White, Res. Pharm., (408) 298-3900, ext. 107; to register by mail: Nutritional Seminar, P.O. Box 970, Cupertino 95014.

February 25-28—**Orthopedic Emergencies.** See Emergency Medicine, February 25-28.

March 10-14—**Controversial Areas in Surgery.** UCLA at Canyon Hotel, Palm Springs. Saturday-Wednesday

March 11-13—**Basic Science for Surgeons.** STAN at Del Monte Lodge, Pebble Beach. Sunday-Tuesday. 8 hrs. $125.

March 14-16—**Basic and Advanced Gyn Urology.** See Obstetrics and Gynecology, March 14-16.

March 14-18—**Vascular Surgery.** UCLA at Canyon Hotel, Palm Springs. Wednesday-Sunday.

March 17—**Cataract Surgery and Intraocular Lens Implantation Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Mrs. Lu Hendricks, Jules Stein Eye Inst., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

March 23-25—**Workshop in Soft Tissue Surgery.** UCI at Registry Hotel, Irvine. Friday-Sunday. 20 hrs. $200.

March 29-30—**International Symposium on the Larynx.** See Medicine, March 29-30.

March 29-30—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

April 3-5—**American Laryngological, Rhinological and Otological Society—Annual Meeting.** Century Plaza, Los Angeles. Tuesday-Thursday. 10½ hrs. $40. Contact: R. L. Ruggles, MD, Exec. Sec., 2954 Dorman Rd., Bromall, PA 19008.

April 5-7—**General Surgery.** UCSF at Sheraton Palace, San Francisco. Thursday-Saturday.

April 8-11—**U.S. Intraocular Lens Symposium.** American Intraocular Implant Society at Century Plaza Hotel, Los Angeles. Sunday-Wednesday. Contact: Kenneth J. Hoffer, MD, P.O. Box 3140, Santa Monica 90403.

April 11—**Diagnosis of the Acute Abdomen.** LLU. Wednesday. 4 hrs.

April 13-14—**Operative Arthroscopy.** UCLA. Friday-Saturday. 12¼ hrs. $315.

April 18-20—**Vitrectomy.** UCSF. Wednesday-Friday.

April 19-20—**Neuro-Ophthalmology—10th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. 16 hrs. $225. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Inst., UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

April 19-21—**Wound Management Workshop.** UCSD, Div. of Plastic Surgery, at Islandia Hyatt House, San Diego. Thursday-Saturday.

April 27-29—**Surgical Update.** UCD at Hyatt Lake Tahoe, Incline Village. Friday-Sunday. 9¼ hrs.

May 10-11—**Surface Replacement.** UCLA. Thursday-Friday.

May 17-18—**Office Orthopedics.** USC. Thursday-Friday.

May 26—**Retinal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Jules Stein Eye Inst., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

May 31-June 1—**Neurosurgery—9th Annual Postgraduate Course.** UCSF at Hilton Hotel, San Francisco. Thursday-Friday.

June 9—**Update of Pediatric Ophthalmology.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $75. Contact: Mrs. Lu Hendricks, Jules Stein Eye Inst., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

June 14-16—**Highlights of Ophthalmology.** PMC. Thursday-Saturday. 15 hrs.

July 23-24—**Microcirculatory Approach to Current Medical and Surgical Problems.** See Medicine, July 23-24.

August 4-11—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 28 hrs. $325.

OF INTEREST TO ALL PHYSICIANS

February 15-December 13—**Differential Diagnosis.** USC. 8 Thursdays.

February 20, 27—**Stress Management in Clinical Practice.** UCLA and Center for Integral Medicine at UCLA. 2 Tuesdays; 7:00-9:30 p.m. $95.

February 21—**Hospital Infections 1979—The Employee, the Patient, the Hospital.** Memorial Hospital Medical Center, Long Beach. Wednesday. 8 hrs. $40. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

February 21-23—**Human Chlamydial Infection and Associated Sexually Transmitted Diseases.** UCSF. Wednesday-Friday.

February 25-March 2—**International Society for Clinical Enzymology.** UCSD at Sheraton Harbor Hotel, San Diego. Sunday-Friday.

February 26-March 2—**Basic Science for Clinicians.** STAN. Monday-Friday. 25½ hrs. $290.

March 2—**Diabetes Program—6th Annual.** UCD at Red Lion Motor Inn, Sacramento. Friday. 6½ hrs. $45.

March 3—**The Borderline: Patient and Family.** Del Amo Hospital, Torrance. Saturday. 6½ hrs. $25. Contact: Community Relations, Del Amo Hospital, 3270 W. Lomita Blvd., Torrance 90505. (213) 530-1151.

March 6-10—**Sports Medicine.** Univ. of Hawaii and AAFP at Princess Kaiulani Hotel, Waikiki, Honolulu. Tuesday-Saturday. 18 hrs. $200. Contact: Hawaii Conference Services. P.O. Box 25055, Honolulu 96825. (808) 377-6445.

March 8-10—**Neurology for Non-Neurologists.** UCSD at Hilton Hotel, San Diego. Thursday-Saturday. 21 hrs.

March 9-10—**Workshop on Aging.** UCD at Hyatt Lake Tahoe, Incline Village. Friday-Saturday. 8 hrs. $85.

March 9-14—**California Medical Association—108th Annual Session.** Bonaventure Hotel, Los Angeles. Friday-Wednesday. Contact: Rocki Lai, CMA.

March 11-15—**The Patient—The Physician—The Process: Appropriate Medicine 1979.** UCLA at Asilomar, Monterey. Sunday-Thursday.

March 14-18—**Preventive Interventions in Medicine: Prenatal to Postmenopause.** Eisenhower Medical Center at Marriott Las Palmas Resort, Rancho Mirage. Wednesday-Sunday. Contact: John J. Deller, MD, Dir. of Ed. and Research, EMC, 39000 Bob Hope Dr., Palm Desert 92260. (714) 346-3911.

March 18-22—**Current Issues in Sexuality in Medical Practice.** UCSF at Yosemite. Sunday-Thursday.

March 22-25—**Basic Clinical Hypnosis Workshop—3rd Annual.** UCI at Balboa Bay Club, Newport Beach. Thursday-Sunday.

March 23-25—**Clinical Management of Anxiety and Stress.** See Psychiatry, March 23-25.

March 29-31—**Contemporary Management of Acute Myocardial Infarction by the Family Physician.** See Medicine, March 29-31.

March 31-April 1—**Symposium on Aging—2nd Annual.** UCSF at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF, Cont. Ed. in Health Sciences, 1343 3rd Ave., San Francisco 94143. (415) 666-3904.

March 31-April 1—**Major Sexually Transmitted Diseases: Biology, Host Response, Diagnosis, Epidemiology and Treatment.** UCLA. Saturday-Sunday.

April 5-7—**West Coast Counties Postgraduate Institute.** CMA and UCD at Doubletree Inn, Monterey. Thursday-Saurday. 13 hrs. $60, CMA members; $90, nonmembers. Contact: Charlotte Newhart, CMA.

April 19-21—**San Joaquin Valley Counties Postgraduate Institute.** CMA and UCSD at Ahwahnee Hotel, Yosemite. Thursday-Saturday. 14 hrs. $60, members; $90, nonmembers. Contact: Charlotte Newhart, CMA.

April 21—**Diagnostic Imaging for Primary Care Physicians.** PMC. Saturday. 6 hrs. $65.

April 21-22—**How Primary Care Physicians Can Enhance Their Patients' Health.** UCLA. Saturday-Sunday.

April 23-25—**The Body Fluids in Health and Disease.** UCSF. Monday-Wednesday.

April 28-May 5—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $325.

April 29-May 4—**American Occupational Medical Association—Annual Meeting.** Disneyland Hotel, Anaheim. Sunday-Friday

16½ hrs. $45, members; $65, nonmembers. Contact: Howard N. Schulz, Exec. Dir., AOMA, 150 N. Wacker Dr., Chicago 60606. (312) 782-2166.

May 4-5—**Providence Hospital Annual Spring Seminar.** Oakland. Friday-Saturday. Contact: Nancy Hansen, Coordinator, Med. Staff Services, Providence Hospital, 3012 Summit St., Oakland 94623. (415) 835-4500, ext. 373.

May 15-21—**Diving Medicine, Basic.** UCSF at VA Hospital, Fresno. One week.

May 18-19—**UCSF—Alumni Day Program.** Friday-Saturday.

May 19-20—**Basic Skills in Sexual Counseling.** UCLA. Saturday-Sunday.

May 20-25—**Fingers-to-the-Toes: An Orthopedic Approach for the Family Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf. Sunday-Friday. 40 hrs. $225.

May 25-26—**Imported Tropical Disease: Current Views on Therapy and Epidemiology.** UCSF. Friday-Saturday.

June 1-2—**Psychosocial Care of the Dying Patient.** See Psychiatry, June 1-2.

June 7-9—**Metabolic and Nutritional Care of the Hospitalized Patient.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Saturday.

June 8-9—**Management of Medical Problems.** PMC. Friday-Saturday. 15 hrs.

June 11-16—**Family Practice Refresher Course.** UCI at South Coast Plaza Hotel, Costa Mesa. One week. 46 hrs. $290.

June 18-22—**Family Practice Symposium.** UCSD at Islandia Hyatt, San Diego. Monday-Friday.

June 23-30—**Manipulative Medicine.** USC at Sheraton-Waikiki, Hawaii. One week. $325.

August 11-22—**Postgraduate Refresher Course—22nd Annual.** USC at Honolulu and Maui or Kauai, Hawaii. Two weeks. 39 hrs. $325.

August 19-25—**Family Practice Refresher Course—7th Annual.** UCD at Del Monte Hyatt, Monterey. One week. 30 hrs. $225.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

OREGON

COUNCIL ON MEDICAL EDUCATION

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, 97213.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

February 12-16—**Tenth Annual Family Practice Review.** Sheraton Hotel, Lloyd Center, Portland. Contact: J. S. Reinschmidt, MD, Director of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OTOLARYNGOLOGY

March 9-10—**Oregon Academy of Otolaryngology 38th Annual Postgraduate Convention.** Thunderbird Motor Inn, Jantzen Beach, Portland. Contact: Miss Rebecca Tarshis, Executive Secretary, PO Box 13155, Portland 97213.

OF INTEREST TO ALL PHYSICIANS

Circuit Course Programs—Contact: Joyce Gullixson, Oregon Medical Association, 5210 SW Corbett Avenue, Portland 97201.

March 1 (Pendleton)—**Office Psychiatric Problems.** St. Anthony Hospital, 1:00 p.m.

March 8 (Astoria)—**Office Gynecology.** Columbia Memorial Hospital 1:30 p.m.

April 11 (Roseburg)—**Urology.** Douglas Community Hospital, 1:30 p.m.

April 12 (Coos Bay)—**Urology.** Thunderbird Courtel, 1:30 p.m.

March 9-10—**Breast Cancer.** Salishan Lodge, Gleneden Beach. Contact: Myrna Glenn, American Cancer Society, 910 NE Union, Portland 97232.

March 28-31—**Common Sense in Comprehensive Care—30th Annual Western Institute on Epilepsy.** Thunderbird Motor Inn, Jantzen Beach, Portland. Contact: Bette Stokes, Epilepsy Association of Oregon, 718 West Burnside, Portland 97209.

March 30-April 1—**Endocrinology.** Salishan Lodge, Gleneden Beach. Contact: J. S. Reinschmidt, MD, Dept. of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

April 4-6—**1979 School of Medicine Alumni Association Scientific Meeting.** University of Oregon Health Sciences Center, Portland. Contact: Mary Ann A. Lockwood, School of Medicine Alumni Association, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

April 19-20—**Dermatology for the Non-Dermatologist.** Red Lion, Jantzen Beach, Portland. Contact: J. S. Reinschmidt, MD, Dept. of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

April 26-27—**Oregon Heart Association Annual Scientific Session.** Red Lion, Portland Center, Portland. Contact: Audrey Booth, Oregon Heart Association, 1500 SW 12th Avenue, Portland 97201.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

March 1-2—**Clinical Allergy for Practicing Physicians.** Thursday-Friday. Seattle. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 9-10—**Pharmacology for the Practitioner.** Friday-Saturday. Virginia Mason Medical Center. Seattle. Contact Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

March 13—**Pediatric Infectious Diseases—Univ. of Wash. Pediatrics Sessions.** Tuesday, 12-1 p.m. Sacred Heart Medical Center, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

March 14-17—**Advances in Pediatrics—118th Meeting North Pacific Pediatric Society.** Wednesday through Saturday. Four Seasons Hotel, Vancouver, BC. Contact: North Pacific Pediatric Society, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

March 15-16—**Internal Medicine.** Thursday-Friday. St. Joseph Hospital, Tacoma. Contact: Maxine Bailey, College of Medical Education, 1500 North Warner, Tacoma, WA 98416. (206) 756-3152.

March 17-24—**Orthopaedics (Basic) and Orthopaedics (Advanced).** Saturday through Saturday. Both at Sun Valley, Idaho. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-0150.

March 19-23—**Advances in Family Practice.** Monday-Friday. Seattle. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 20—**Infectious Diseases—Univ. of Wash. OB-GYN Sessions.** Tuesday, 12-1 p.m., Sacred Heart Medical Center, Spokane. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

March 21—**A Day of Pediatrics.** Wednesday. Mary Bridge Children's Hospital, Tacoma. Contact: Maxine Bailey, College of Medical Education, 1500 North Warner, Tacoma, WA 98416. (206) 756-3152.

March 26-27—**Breast Cancer.** Monday- Tuesday. Swedish Hospital Medical Center, Seattle. Contact: John L. Wright, MD, Swedish Hospital Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2265.

March 26-27—**Nutrition 1979—Univ. of Wash. Internal Medicine Review Sessions.**

March 26, Monday, 7:30-9:30 p.m. Wenatchee Valley Clinic, Wenatchee. Contact: William McKee, MD, Wenatchee Valley Clinic, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 27, Tuesday, 5-7 p.m. Memorial Hospital, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

March 29-30—**Hematology for Primary Care Physicians.** Thursday-Friday. Seattle. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 2-13—**Rehabilitation Medicine Review.** Two-week course, Seattle. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 7—**Mason Clinic Day.** Saturday. Virginia Mason Medical Center, Seattle. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

April 9-13—**Obstetrics/Gynecology Review.** Monday-Friday. Hyatt Regency, Waikiki, Hawaii. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 10—**Univ. of Wash. Pediatrics Sessions.** Tuesday, 12-1 p.m., Sacred Heart Medical Center, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

April 16-21—**Spanish for Health Professionals.** Monday-Saturday. Seattle. U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 17—**Intrauterine Growth and Retardation—Univ. of Wash. OB-GYN Sessions.** Tuesday, 12-1 p.m., Sacred Heart Medical Center, Spokane. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

April 23-24—**Drug Interactions—Univ. of Wash. Internal Medicine Review Sessions.**

April 23—Monday, 7:30-9:30 p.m., Wenatchee Valley Clinic, Wenatchee. Contact: William McKee, MD, Wenatchee Valley Clinic, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

April 24, Tuesday, 5-7 p.m., Memorial Hospital, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

April 26—**Hypertension Update.** Thursday. Seattle. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 28—**Medicine—Tacoma General Hospital Day.** Wednesday. Tacoma General Hospital, Tacoma. Contact: Maxine Bailey, College of Medical Education, 1500 North Warner Tacoma, WA 98416. (206) 756-3152.

May 3-4—**Medical Alumni Days.** Thursday-Friday. Seattle. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 4-5—**Medical Applications of Real Time Ultrasound.** Friday-Saturday. Virginia Mason Medical Center, Seattle. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 7-8—**Management of Birth Defects.** Monday-Tuesday. Seattle. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 11—**Participation Seminar: Management of Cirrhosis of the Liver.** Friday. Virginia Mason Medical Center, Seattle. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 14-15—**Immunoglobulins and Immunologic Disease—Univ. of Wash. Internal Medicine Review Sessions.**

May 14, Monday, 7:30-9:30 p.m., Wenatchee Valley Clinic, Wenatchee. Contact: William McKee, MD, Wenatchee Valley Clinic, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 15, Tuesday, 5-7 p.m., Memorial Hospital, Yakima. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

May 15—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions.** Tuesday 12-1 p.m., Sacred Heart Medical Center, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

May 18-19—**Radiology.** Friday-Saturday. White Pass Mountain Resort. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 19-20—**Extracapsular Cataract Surgery and Artificial Lens Implantation: The Northwest Course.** Saturday-Sunday. Overlake Hospital, Bellevue. Contact: David J. McIntyre, MD, Northwest Microsurgical Institute, Inc., 1035 116th Ave., NE, Bellevue, WA 98004. (206) 454-7912.

May 22—**Gynecologic Cancer—Univ. of Wash. OB-GYN Sessions.** Tuesday, 12-1 p.m., Sacred Heart Medical Center, Spokane. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 31 and June 1—**Respiratory Care.** Thursday-Friday. Seattle. Contact U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 1—**Management of Acute Surgical Problems.** Friday. Virginia Mason Medical Center, Seattle. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 2-3—**Colon and Rectal Surgery.** Saturday-Sunday. Washington Plaza Hotel, Seattle. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 7-8—**Surgery.** Thursday-Friday. Seattle. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 21-23—**American College of Cardiology: Medical and Surgical Management of Coronary Artery Disease.** Thursday-Saturday. Virginia Mason Medical Center, Seattle. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 23-24—**Medical History.** Saturday-Sunday. Sun Valley, Idaho. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 25-26—**Platelets and Clotting—Univ. of Wash. Internal Medicine Review Sessions.**

June 25—Monday, 7:30-9:30 p.m., Wenatchee Valley Clinic, Wenatchee. Contact: William McKee, MD, Wenatchee Valley Clinic, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

June 26, Tuesday, 5-7 p.m., Memorial Hospital, Yakima. Contact: Harry Kimball, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

ALASKA, MONTANA AND IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

May 10—**Consultation With the Alaskan Native Child—Univ. of Wash. Psychiatry Sessions.** Thursday. Anchorage: Contact: Robert F. Kraus, MD, Star Route A, Box 26-B, Anchorage, AK 99507. (907) 344-7863.

MONTANA

February 14-15—**Pediatric Hematology—Univ. of Wash. Pediatrics Sessions.**

Feb. 14, Wednesday, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

Feb. 15, Thursday, Whitefish/Kalispell. Contact: Ronald Miller, MD, 4th and Baker, Whitefish, MT 59937. (406) 862-2515.

February 28-March 2—**Pulmonary Embolism and Asthma. Univ. of Wash. Internal Medicine Review Sessions.**

Feb. 28, Wednesday, Great Falls. 5-7:30 p.m. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 1, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 2, Friday, Missoula. 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

March 1-3—**GYN Cancers.** Thursday-Saturday. Big Sky. 12 hrs. Fee: $30. Contact: Western Montana Health Education Council, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

March 2-3—**Montana Cardiologists' Seminar.** Friday-Saturday. Big Sky. Fee: $15. Contact: Western Montana Health Education Council, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

March 9-10—**Drug Therapy: A Review of Basic and Clinical Pharmacology in Practice.** Friday-Saturday. Big Sky. 8 hrs. Fee: $50. Contact: Interhospital Continuing Education Department, Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 14-15—**Pediatric Infectious Diseases—Univ. of Wash. Pediatrics Sessions.**

March 14, Wednesday, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 15, Thursday, Whitefish/Kalispell. Contact: Ronald Miller, MD, 4th and Baker, Whitefish, MT 59937. (406) 862-2515.

March 28-30—**An Approach to the Cutaneous Manifestations of Internal Malignancy—Univ. of Wash. Internal Medicine Review Sessions.**

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: June 6-8, 1979, Shee Atika Lodge, Sitka.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 25-29, 1979, Safari Hotel, Scottsdale.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 9-12, 1979, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 19-23, 1979, the Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 8-12, 1979, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: 1979—date and place to be announced.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 4-6, 1979, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 18-20, 1979, Ely Convention Center, Ely.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 2-4, 1979, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Meeting of House of Delegates: April 20-22, 1979, Valley River Inn, Eugene. Annual Scientific Meeting: November 2-4, 1979, OMA Headquarters.

Utah State Medical Association—42 S. 5th East St., Salt Lake City 84102. Annual Meeting: September 11-14, 1979, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 4-7, 1979, Washington Plaza Hotel, Seattle.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: August 28-31, 1979, Jackson Lake Lodge, Moran.

March 28, Wednesday, Great Falls. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 29, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 30, Friday, Missoula. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

IDAHO

February 20-21—**Pediatric Hematology—Univ. of Wash. Pediatrics Sessions.**

Feb. 20, Tuesday, Pocatello. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

Feb. 21, Wednesday, Boise. 9-10 a.m., Anderson Center. Contact: Thomas Cornwall, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 377-4400.

February 22-25—**Internal Medicine Residents' Second Annual Winter Retreat.** Thursday-Sunday. Shore Lodge, McCall. Contact: James Hammarsten, MD, Veterans Administration Hospital, 5th and Fort Sts., Boise, ID 83702. (208) 336-5100.

March 2-4—**Ada County and Southwest Idaho Medical Societies' Winter Clinics.** Friday-Sunday. McCall. Hours and fee to be determined. Contact: Ada County Medical Education Consortium, 190 East Bannock, Boise, ID 83702. (208) 386-2135.

March 19—**Infectious Disease—Univ. of Wash. OB-GYN Sessions.** Monday. 12-1 p.m., St. Luke's Hospital, Boise. Contact: David Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391.

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March 21, Wednesday, Boise. 9-10 a.m., Anderson Center. Contact: Thomas Cornwall, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 377-4400.

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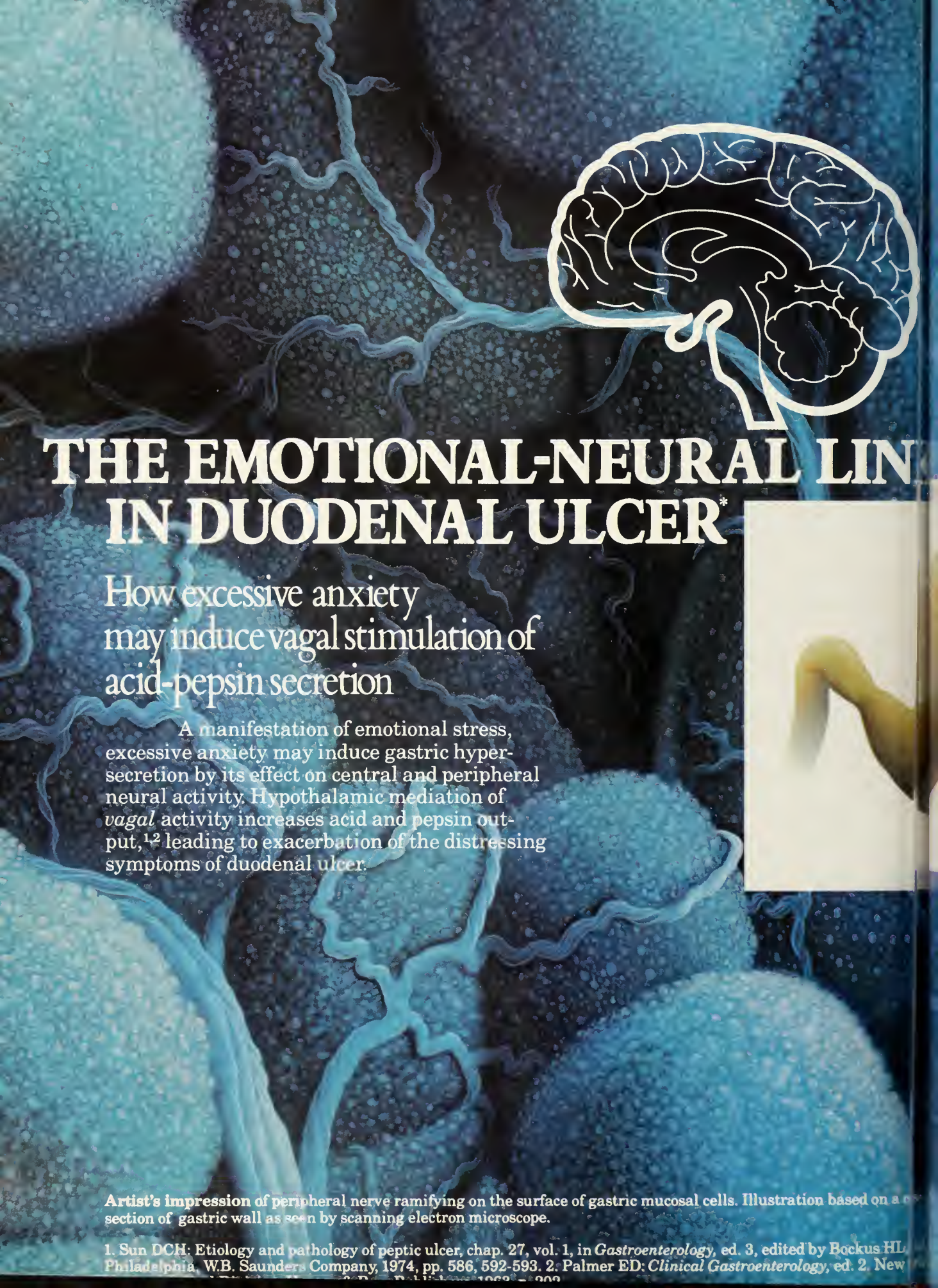

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Artist's impression of peripheral nerve ramifying on the surface of gastric mucosal cells. Illustration based on a c section of gastric wall as seen by scanning electron microscope.

1. Sun DCH: Etiology and pathology of peptic ulcer, chap. 27, vol. 1, in *Gastroenterology*, ed. 3, edited by Bockus HL, Philadelphia, W.B. Saunders Company, 1974, pp. 586, 592-593. 2. Palmer ED: *Clinical Gastroenterology*, ed. 2, New

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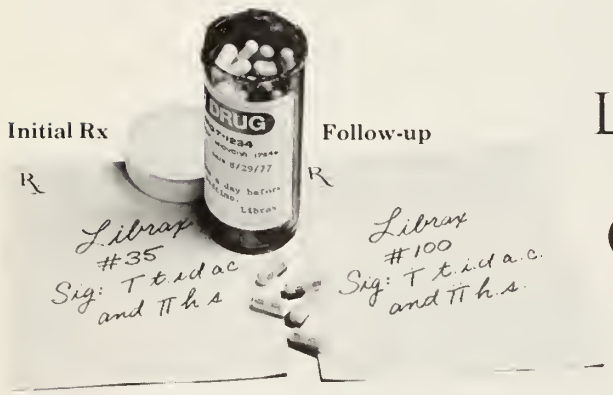

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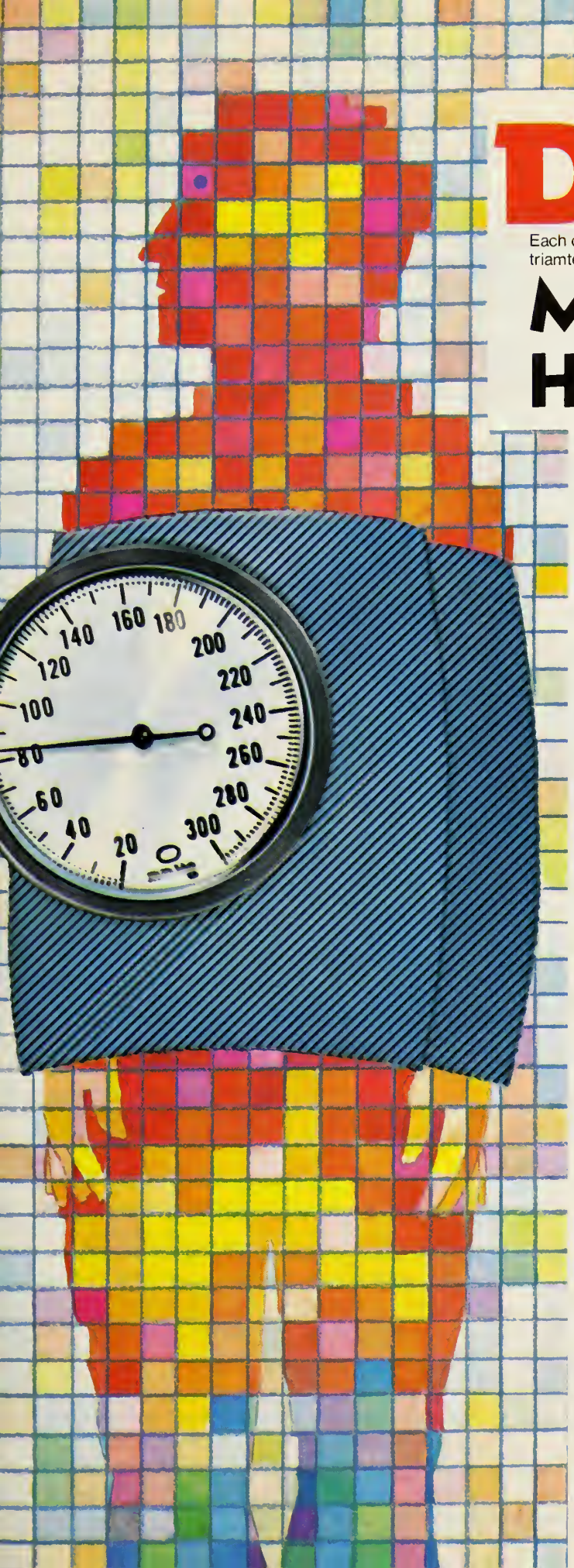

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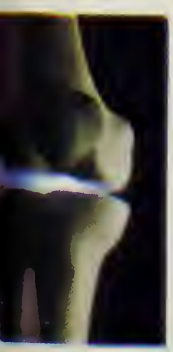
So it is not surprising that in this short period Motrin has become the most frequently prescribed alternative to aspirin. Motrin relieves joint pain and inflammation as effectively as indomethacin or aspirin, but causes significantly fewer CNS and milder GI reactions. However, gastrointestinal bleeding, sometimes severe, has been associated with Motrin, aspirin, indomethacin, and other nonsteroidal antiarthritic agents.

*The safety and effectiveness of Motrin have not been established in patients with Functional Class IV rheumatoid arthritis (incapacitated, largely or wholly bedridden, or confined to wheelchair; little or no self-care).



Motrin 400 mg TABLETS
ibuprofen, Upjohn

The confidence that comes from experience—one more reason to prescribe Motrin.

Please turn page for a brief summary of prescribing information.

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001

The confidence that comes from experience—
one more reason to prescribe

Motrin 400 mg TABLETS
ibuprofen, Upjohn

Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin* used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin (ibuprofen) is gastrointestinal (4% to 16%). This includes nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness*, headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

Incidence: Unmarked 1% to 3%; *3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

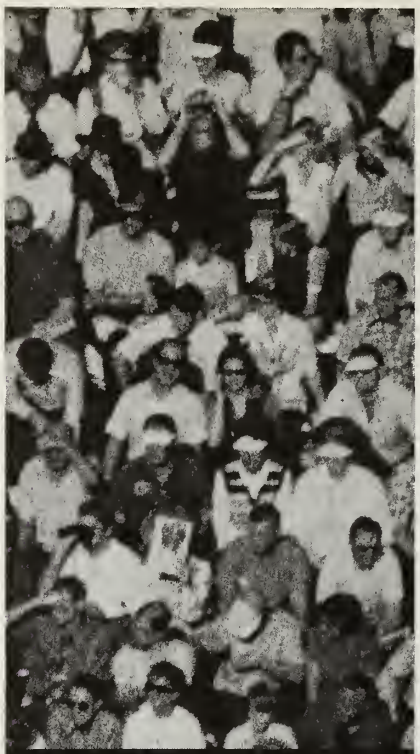
Dosage and Administration: Suggested dosage is 300 or 400 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day.

How Supplied

Motrin Tablets, 300 mg (white)	
Bottles of 60	NDC 0009-0733-01
Bottles of 500	NDC 0009-0733-02
Motrin Tablets, 400 mg (orange)	
Bottles of 60	NDC 0009-0750-01
Bottles of 500	NDC 0009-0750-02
Unit-dose package of 100	NDC 0009-0750-06
Unit of Use bottles of 120	NDC 0009-0750-26

Caution: Federal law prohibits dispensing without prescription.

NIM-3



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100	Equanil (400 mg.) C IV	8.09	Meprobamate (100 mg.) C IV	**1.83**	**6.26**
100	Darvon Comp. 65 C	7.83	Propoxyphene HCl Comp. 65 C	**4.63**	**3.20**
100	Pavabid (150 mg.)	11.73	Papaverine HCl T.R. (100 mg.)	**4.33**	**7.40**
100	Thorazine (50 mg.)	6.03	Chlorpromazine HCl (50 mg.)	**3.23**	**2.80**
100	Librium (10 mg.) C IV	7.11	Chlordiazepoxide HCl (10 mg.) C IV	**4.89**	**2.22**

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INFORMATION

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EX 220

Tablets

PERCOCET®-5 (II)

Brief Summary of Prescribing Information

DESCRIPTION Each tablet of PERCOCET®-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS. 6085 BS

DEA Order Form Required.

PERCOCET® is a U.S. registered trademark of Endo Inc.

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Manati, Puerto Rico 00701
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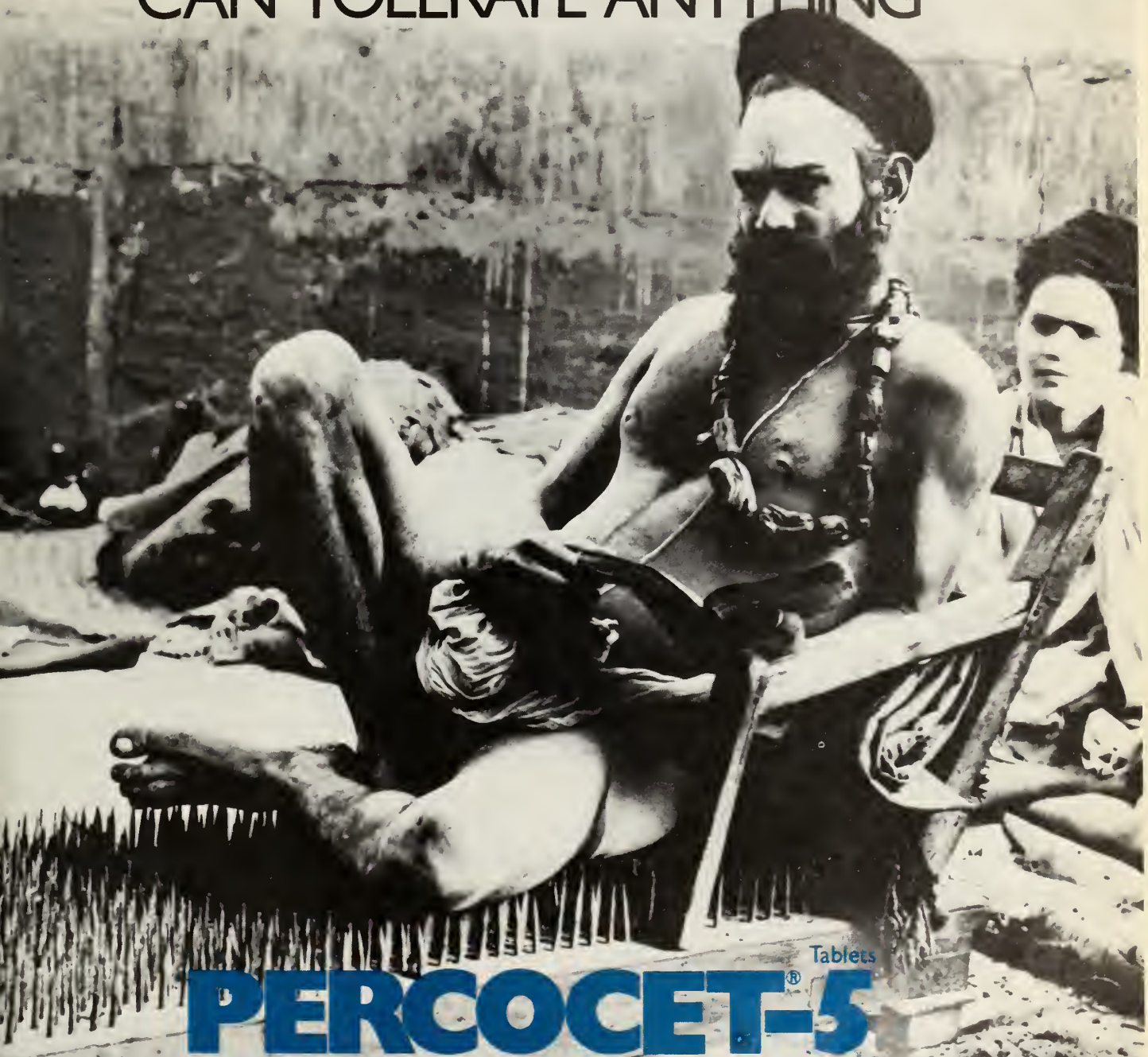
DUPONT

SOME PEOPLE CAN TOLERATE ANYTHING



Tablets

PERCOCET®-5

Each tablet contains 5 mg oxycodone HCl (WARNING: May be habit forming) and 325 mg acetaminophen (APAP) CII

..FOR THOSE WHO CAN'T TOLERATE ASPIRIN

- □ indicated for moderate to moderately severe pain
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Please see opposite page for brief summary of prescribing information.

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It could well be the answer for many people who rely on you for their dietary needs, those with an allergy similar to Steve's, or a lactose intolerance. And, for many who must maintain a fat-restricted diet you should know that Mocha Mix is one non-dairy creamer that contains no coconut oil, giving it the highest ratio of unsaturated to saturated fat of any creamer. It easily exceeds the accepted standard 2:1 ratio. It's 100% cholesterol free, too. No wonder Mocha Mix is not just another non-dairy creamer, but the one you can rely on most for your patients who can't speak for milk, either.

NUTRITION INFORMATION

Portion Size 1 Fluid Ounce (2 Tbs.)	
Servings Per Container	16
Calories	40
Protein	0 grams
Carbohydrate	3 grams
Fat	3 grams
Percent of Calories from Fat	73%
Polyunsaturated Fat	1 gram
Saturated Fat	0 grams
Cholesterol (Δ)	0 mg (0 mg/100g)

In addition to the pint and quart size found in the dairy case of most grocery stores, Mocha Mix is available in 4 ounce and ½ oz. portion packs for hospitals and institutions.

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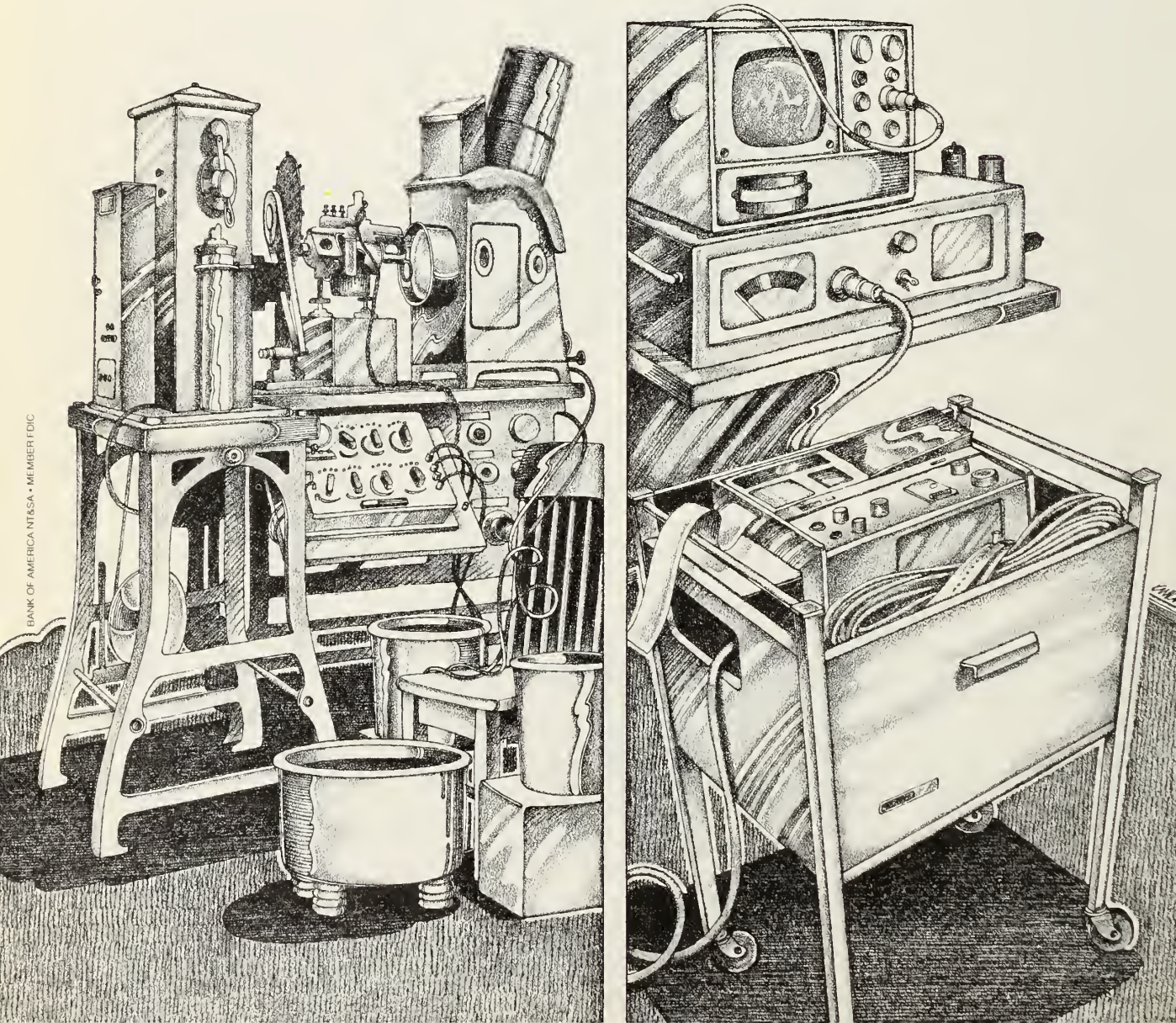

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THE WESTERN
Journal of Medicine

Refer to: Silverberg GD, Britt RH: Transsphenoidal hypophysectomy in the treatment of metastatic breast and prostate carcinoma. West J Med 130:191-195, Mar 1979

Transsphenoidal Hypophysectomy in the Treatment of Metastatic Breast and Prostate Carcinoma

GERALD D. SILVERBERG, MD, *and* RICHARD H. BRITT, MD, *Stanford, California*

The cases of 70 consecutive patients having a transsphenoidal hypophysectomy for metastatic carcinoma of the breast or prostate are reviewed. In half of the patients with cancer of the breast an objective remission was obtained. In 30 percent of the patients with cancer of the prostate there were objective signs of tumor regression and in 75 percent there was relief of pain. The operative mortality was 1.4 percent and the morbidity of the procedure was gratifyingly small. There is some indication that hypophysectomy may be preferred to adrenalectomy in patients with hormone-responsive metastatic mammary cancer.

In 1957 Luft and Olivecrona[1] reported that somewhat more than 50 percent of their patients suffering from metastatic cancer of the breast or prostate were benefitted by hypophysectomy. Despite significant recent advances in chemotherapy, hormonal ablation still remains one of the most effective means of achieving palliation in patients with hormone-dependent metastatic tumors of the breast and prostate.[2] Omitting those premenopausal women who did not respond to oophorectomy, one can expect a response rate of about 40 percent to 50 percent after hypophysectomy.[3]

It is possible to increase the success rate of hormonal ablation in women with metastatic cancer of the breast by judicious selection of patients; that is, patients with one organ system involved tend to respond more favorably than those with multiple systems invaded by tumor.[4] Patients with a long clinically-free interval from the time of initial diagnosis to the first sign of metastatic disease seem to respond more often than patients with more rapidly metastatic tumors.[5] Older patients with more indolent disease appear to fare better than younger patients with more aggressive tumors.[2] A previous response to hormone therapy seems to be predictive of a favorable outcome to hormonal ablation,[6,7] though this is contested by some.[4] If one is able to assess the presence of estrogen binding by the patient's tumor cells and select for hypophysectomy only those patients in whom significant binding is shown, then the response rate increases to about 60 percent to 80 percent.[8-11] Duration of response will vary from six months to several years.[3,6]

In men suffering from metastatic cancer of the prostate, significant benefit may result from hy-

From the Division of Neurosurgery, Stanford University Medical Center, Stanford, California.

Submitted August 31, 1978.

Reprint requests to: Gerald D. Silverberg, MD, Division of Neurosurgery (Room R155), Stanford University Medical Center, 300 Pasteur Drive, Stanford, CA 94305.

pophysectomy after control of tumor by therapy with estrogens or castration, or both, fails. In about 70 percent of such patients there will be relief of pain, though in only 30 percent will there be objective regression of tumor and a prolonged survival.[12] Unfortunately, the duration of response and survival in these patients appears to be less than in those patients with cancer of the breast in whom there is response.

Despite substantial evidence to support the effectiveness of hypophysectomy in palliating disease in such patients, many physicians are reluctant to subject patients with a terminal illness to an operative procedure. We have reviewed our experience with transsphenoidal hypophysectomy at Stanford in the treatment of metastatic cancer of the breast and prostate to evaluate the safety and effectiveness of this form of therapy.

Methods

The cases of the first 70 consecutive patients in whom transsphenoidal hypophysectomy was carried out for cancer of the breast or prostate were reviewed. The ages of the 42 women with metastatic cancer of the breast were 31 to 78 years (mean age, 55 years); 79 percent were postmenopausal, 12 percent were within one year of menopause and 9 percent were still menstruating regularly. In 83 percent multiple systems were involved by metastatic cancer of the breast, while in only 17 percent was the disease confined to one system, usually bone.

The mean age of the 28 men with cancer of the prostate was 67 years (range, 47 to 81 years). Diffuse bony metastases were present in all patients, and bone pain was the principal reason for pituitary ablation in all but one patient who had a carcinomatous neuromyopathy. In all there had been either failure or relapse from treatment with estrogens or castration, or both. Most had had both pelvic irradiation and palliative irradiation to metastatic sites.

In patients with cancer of the breast, remission was defined as objective regression of tumor or arrest of tumor progression (in patients with obvious progression of disease before hypophysectomy) for six months without the appearance of new lesions. Tumor regression was determined by clinical examination (palpable shrinkage of tumor masses), x-ray studies and scan imaging, and confirmed by results of laboratory studies (serum alkaline phosphatase, serum calcium, liver function studies and the like) where these values were abnormal before pituitary ablation. Subjective improvement, such as relief of pain, increased appetite and weight gain, usually accompanied the objective signs of regression but were not used to determine response. Objective regression was more difficult to document in the patients with cancer of the prostate because the disease was usually confined to bone, and changes shown on x-ray studies were difficult to interpret. However, we could document regression of pleural or pulmonary lesions and shrinkage in the prostate mass, as well as relief of spinal cord compression, ureteral obstruction and peripheral nerve compression in some patients. Acid phosphatase levels, when they returned to normal, were also a good sign of regression in contrast to alkaline phosphatase levels which were not.[12]

The open transsphenoidal technique, using the operating microscope to deliver the entire pituitary gland, was used. At present we admit the patient the day before the operation for preparation. Bacitracin nose drops (50,000 units in 1 dl of normal saline), three or four drops in each nostril, are administered at intervals of six hours, and half-strength hydrogen peroxide mouthwashes are used four times that day. Ampicillin, 2 grams given by mouth in divided doses, is also used. Hydrocortisone, 100 mg, is given intramuscularly the night before and the morning of the operation as well as intravenously during the operation along with 1 gram of ampicillin. We use the sublabial approach as described by Hardy[13] except that we do not excise the nasal septum. We simply detach the inferior margin and swing it to one side. After delivering the gland, we treat the sella with absorbable gelatin sponge (Gelfoam) pledgets soaked in absolute alcohol. We then pack the sella by making a pouch of lyophilized dura* and stuffing it with fat, the whole packing being held in place by a piece of tantalum wire mesh slipped inside the opening of the sella floor. If a leak of cerebrospinal fluid (CSF) is encountered, then another piece of lyophilized dura is placed over the outside of the sella floor and held in place with either more fat or Gelfoam soaked in bacitracin. Two fingers of a surgical glove are coated with bacitracin ointment, placed in the nose and packed with half inch vaginal packing soaked with bacitracin ointment. The nasal packs are removed in 24 hours. Postoperatively the hydrocortisone is rapidly tapered to a maintenance dose over four

*Obtained from the Tissue Bank, Santa Clara Valley Medical Center, San Jose, California.

TABLE 1.—*Complications of Transsphenoidal Hypophysectomy in 70 Patients*

	Number of Patients	*Percent*
Operative deaths	1	1.4
Cerebrospinal fluid leaks	3	4.3
Meningitis	2	2.9
Carotid laceration	1	1.4
Pneumonia	1	1.4
Gastrointestinal bleeding	1	1.4
Hypoglycemia	1	1.4

days, and the patients are discharged from the hospital on maintenance therapy with hydrocortisone and thyroid replacement. Persistent diabetes insipidus is treated with lypressin (Diapid) nasal spray.

We have not routinely tested for completeness of the hypophysectomy, but in several patients in whom there was no response, growth hormone stimulation was done and no response was noted, suggesting a complete hypophysectomy. One patient in whom there was no response stopped taking hydrocortisone after signing a living will and died in addisonian crisis, suggesting a complete pituitary ablation. Also, premenopausal patients stopped menstruating.

Complications

There was one death (1.4 percent) attributable to surgical operation (Table 1). There was one permanent complication (1.4 percent), a carotid laceration requiring carotid occlusion. The patient had no neurologic sequelae save for a transient sixth nerve palsy, presumably from packing the cavernous sinus. Four patients (5.6 percent) had potentially serious complications, CSF rhinorrhea or meningitis, or both. In the three patients with CSF leaks, reoperation was carried out immediately and the leaks sealed. In the two patients with meningitis, one of whom had no evidence of a CSF leak, there was response to therapy with the appropriate antibiotics. Since adopting our present mode of packing the sella and removing the nasal packs after 24 hours, we have not had any cases of CSF leak or ascending infection. There were three less serious complications (4.2 percent): postoperative pneumonia in a very debilitated elderly man, a gastrointestinal hemorrhage in a patient with known peptic ulcer disease, and an episode of hypoglycemia in a diabetic patient who was found not to require insulin following hypophysectomy. All responded to appropriate therapy.

Diabetes insipidus occurred in nearly all patients postoperatively but was usually over by the time the patient was discharged. In 25 percent of the patients, the diabetes insipidus was of more prolonged duration requiring lypressin nasal spray for control. Frequently the spray was required only at night before bed. In one patient, an elderly man with disseminated prostatic cancer, the lypressin spray did not seem to affect the diabetes insipidus, and parenteral injections of vasopressin in oil were required every two to three days.

Results

Of the 42 patients with mammary cancer, 38 have been followed for longer than six months. In 19 (50 percent) there was objective evidence of response. The mean age of the responders was 51 years. The mean age of the nonresponders was 50 years. We were unable to ascertain any statistically significant difference between the two groups when compared for age, clinically-free interval, number of organ systems involved or tumor histology.

In 20 patients previous hormone manipulation had been carried out: oophorectomy or administration of male or female hormones or their derivatives (excluding corticosteroids). In ten of these there was response—either significant improvement or significant worsening of disease. This included two patients given tamoxifen (Nolvadex, Stuart Pharmaceuticals, Inc., 3411 Silverside Road, P.O. Box 751, Wilmington, Delaware 19897). One worsened on tamoxifen therapy and one improved transiently. In seven of those ten patients there was response to hypophysectomy (70 percent), while in only two of the ten who had not shown any hormone sensitivity was there a good result. In the one patient in whom there was a flare of disease on tamoxifen therapy, objective regression of the tumor occurred. It is still too soon postoperatively to evaluate the condition of the patient in whom there was a transient response. In 16 patients estrogen receptor assays were done. Of these studies, findings were considered positive in nine patients. In seven of these nine patients (78 percent) there was response to hypophysectomy. Conversely, in only two patients with negative receptor assays was there response, and in one of these patients the assay was not done at Stanford but sent to an outside laboratory from a small community hospital. Estrogen receptor assays are very labile and will be falsely negative if the tissue to be assayed

is allowed to stand at room temperature even for a relatively short time.

The mean duration of response was 15 months with a range of 9 to 24 months. Nine responders are still in remission. Of the responders available for follow-up (17 patients), 13 are alive with a mean survival of 17 months (range, 7 to 42 months) since hypophysectomy. Four are dead, with a mean survival also of 17 months (range, 10 to 27 months). The records of 17 patients in whom there was no response to hypophysectomy were followed up. All but one patient was dead. The average survival after hypophysectomy was five months (range, two weeks to 22 months). One patient was still alive six months postoperatively.

The cases of most of the patients with prostatic cancer have already been reported.[12] The addition of 11 more patients did not appreciably change the rate of response. Relief of pain, the primary reason for hypophysectomy in almost all the patients, was achieved in 75 percent of the patients, but objective evidence of tumor regression occurred in only 30 percent. The patients in whom there were objective responses had a longer duration of subjective relief (mean, 11 months) and prolonged survival (mean, 12 months) compared with those in whom there were no objective responses. Those who had only subjective relief of pain had a mean duration of response and survival of only four months, while those who had no response had a mean survival of only two months. There were no clinical criteria found that would have predicted in which patients response would occur, but several factors were found to mitigate against a good response. In patients with severe myelophthisic anemia (hematocrit lower than 30 percent), patients with liver metastases and patients in whom previously there had been no response to therapy with estrogens or castration, an objective remission did not occur. In one interesting case of a patient in whom an operation was done for a neuromyopathy thought to be a remote effect of prostatic cancer, there was significant regression of weakness.

Discussion

Our experience suggests that transsphenoidal hypophysectomy in the treatment of mammary and prostatic cancer is a safe and relatively benign procedure, well tolerated even by old and seriously ill persons. Our remission rate in mammary cancer is better than the 30 percent to 40 percent rates reported in most series of unselected patients treated with adrenalectomy or hypophysectomy. This primarily reflects some degree of selection of patients. It has been estimated that about 50 percent of patients with mammary cancer have hormone-responsive tumors as measured by the estrogen-binding assay.[8] Since 60 percent to 80 percent of these patients can be expected to respond to hormonal ablation, then one would anticipate a 30 percent to 40 percent rate if no selection factors were used. In our series, the selection factors that are clearly of importance are the response to previous hormonal manipulation and the presence of estrogen-binding proteins in the tumor. As others have noted,[9] age, clinically-free interval and dissemination of disease are far less predictive.

It has been stated that the rate and duration of response are the same for both hypophysectomy and adrenalectomy.[2,4] However, there is some evidence that this may not be true. Taylor, in the Joint Committee Report on endocrine ablative procedures,[17] noted that patients who had had a favorable response to oophorectomy had a statistically longer survival after subsequent hypophysectomy than after adrenalectomy. In the only randomized prospective study so far reported, Atkins and co-workers[14-16] found a statistically significant increase in rate, duration of response and survival in those patients in whom hypophysectomy was carried out for metastatic mammary cancer compared with those in whom adrenalectomy was done. Fracchia, in his series from Memorial Hospital comparing 500 patients who had adrenalectomy with 203 patients who had hypophysectomy,[4] noted no significant difference between the two procedures. However, he included within the hypophysectomy group 20 patients in whom adrenalectomy had been done previously. We now know that one can expect a very poor yield from this group. If these cases are omitted, then there would be a higher incidence of response in the patients in whom hypophysectomy is done. It is also interesting to note that of the patients undergoing hypophysectomy, there were 12.3 percent with an objective remission greater than 24 months compared with only 6 percent of the patients in whom adrenalectomy was carried out. Unfortunately, data on survival were not included in this study.

Although the above data suggest that hypophysectomy may be a better hormonal ablation than adrenalectomy, there are not yet enough corrobo-

rative data from other studies to be dogmatic. However, if one reviews the morbidity and mortality of both procedures, it appears that patients are better served by hypophysectomy. Mortality rates for adrenalectomy vary from 1 percent to 9 percent, while the morbidity ranges from 20 percent to 40 percent[5,7,9,18,20] with the major complications being pulmonary. In our experience, hypophysectomy appears to be well-tolerated. Patients are usually up and about and eating within 48 hours. Our series includes a number of patients who were felt to be too ill for adrenalectomy and several in whom an attempt at adrenalectomy had to be abandoned. In five patients there was pronounced respiratory insufficiency from pulmonary metastases, such that they were dyspneic at bedrest. All survived the procedure without postoperative pulmonary problems. It has been argued that patients in whom hypophysectomy has been done are more difficult to maintain postoperatively. We have not found this to be a problem; indeed, the presence of an intact aldosterone response makes hyponatremia much less of a problem in patients after hypophysectomy in contrast to patients after adrenalectomy. Diabetes insipidus in most patients abates before they go home. In those that have persistent diabetes insipidus, it is almost always controlled with lypressin nasal spray and tends to improve with time.

It is not entirely clear why the rate and duration of response, as well as the survival, of patients with metastatic prostatic cancer are less than in those with mammary cancer. The prostatic patients are older, the extent and duration of disease are frequently greater, and we do not yet have a test comparable to the estrogen-binding assay to help select hormone-responsive tumors. However, even if we select only those patients whose tumors have shown previous hormonal sensitivity, there is still a significant difference in response. If we omit the proven hormone nonresponders in our series (14 percent), the objective regression rate is only 35 percent. One must therefore suspect that there is a significant number of nonhormone-responsive tumor cells present along with the dihydrotestosterone-dependent cells, and these are unaffected by hypophysectomy.

Despite the relatively low response rate in prostatic cancer, the very low morbidity and mortality of transsphenoidal hypophysectomy still makes it a worthwhile consideration in those patients who have hormone-responsive tumors, provided the patient does not have liver metastases or severe myelophthisic anemia.

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Nosocomial Varicella

Part I: Outbreak in Oncology Patients at a Children's Hospital

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Twenty cases of varicella occurred in patients or siblings of patients in a 41-day period in a children's hospital. Most cases were among oncology patients, with transmission occurring in both the inpatient and outpatient areas. One patient died after visceral dissemination of varicella. Neither pooled immunoglobulin nor zoster immune plasma was effective in preventing clinical varicella, although zoster immune plasma appeared to ameliorate the illness. Recommended control measures included strict isolation or discharge of infected patients, and respiratory isolation or discharge of exposed susceptibles. Although apparently too late to be effective in this outbreak, similar measures are warranted should nosocomial outbreaks of varicella occur elsewhere.

WHILE VARICELLA is usually a benign disease of childhood, it can cause severe or fatal illness in patients with impaired immunity.[1-4] Nosocomial outbreaks of varicella-zoster illness have resulted in serious morbidity and mortality,[5-10] especially on oncology wards where numerous patients with impaired immunity may be exposed simultaneously.[11] In recent years many pediatric oncology units have combined outpatient, inpatient and intermediate care facilities into "therapeutic communities" to allow patients to enjoy a more normal life style while receiving necessary therapy. However, with the establishment of such therapeutic communities, potential mechanisms for the spread of nosocomial infection have become more complex and, accordingly, more difficult to control. This paper describes an outbreak of 20 cases of varicella in such a unit for pediatric oncology patients, and discusses the control measures that were used in an attempt to halt the spread of varicella.

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Part I of a two-part article. Part II: Suggested Guidelines for Management, will be published in a subsequent issue.

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Background

The Children's Hospital at Stanford University is a 60-bed hospital with four separate inpatient wards, outpatient facilities located within the hospital, and a physically separate but nearby intermediate care facility. Two wards and most beds in the intermediate care facility are used by the oncology service, which is organized as an open therapeutic community. Oncology patients have access to the inpatient units, the intermediate care

facility and the outpatient department unless precluded by medical considerations including infections; parents and other family members may "live in" on the hospital ward. In addition, nononcology patients share the outpatient, intermediate care and inpatient recreational facilities with the oncology patients, and are free to visit the oncology wards.

Methods

The period of varicella communicability in normal persons is variable, though in general communicability is considered to end when all lesions have crusted;[12] however, varicella may occasionally be communicable as early as four days before rash onset in normal children[5] and up to a week or more after rash onset in immunosuppressed patients. Because of these uncertainties regarding the period of communicability in individual patients, the inclusive period of varicella communicability for the purpose of this epidemiologic investigation only was arbitrarily defined as two days before rash onset to five days after rash onset. High risk of exposure to varicella was considered to exist on days when a patient within this communicable period was an inpatient (ward or intermediate care) or attended the outpatient clinic without being isolated. For patients in whom varicella subsequently developed, the likely time of exposure was considered to be between 10 and 21 days before rash onset (usual minimum and maximum incubation periods). Only the month of March was analyzed since isolation procedures were instituted in April. It was necessary to use varicella histories in the estimation of attack rates since preexposure serology findings were not available. The probable source of exposure as described in the text was derived from dates of inpatient admissions and outpatient visits as well as from available information about community exposures.

Results

The Outbreak

Between March 6 and April 20, a total of 20 cases of varicella occurred among patients and their siblings (See Figure 1). Fourteen cases were in oncology patients, four in their normal siblings and two in nononcology patients. In two oncology patients hemorrhagic varicella developed, and another died with visceral dissemination of varicella five days after onset.

The index case and the next three cases (one in a nononcology patient) occurred in children who had been exposed during the customary peak of varicella activity in the general community, though two of the latter cases may also have been exposed to the index patient on his day of admission. Of the 11 subsequent cases in oncology patients, ten occurred after nosocomial exposure. Only one of these ten patients had had any possible community exposure. In the 11th case, the patient had a known community exposure. Three of the four cases among siblings also occurred after hospital exposure; none had a known exposure in the community. Both nononcology patients had been inpatients during periods of potential risk but one had also been exposed in the community as noted above. In both, varicella developed after discharge, and no additional cases occurred in nononcology patients.

Forty-three oncology patients were exposed on at least one high-risk inhospital day. Eight cases of varicella developed among this group, for an overall attack rate of 19 percent. Of these 43 oncology patients, 21 were historically susceptible to varicella at the time of exposure, and all eight cases occurred in this group, for an attack rate of 38 percent. No cases appeared among the 22 oncology inpatients with a history of previous varicella.

A total of 104 oncology patients attended the

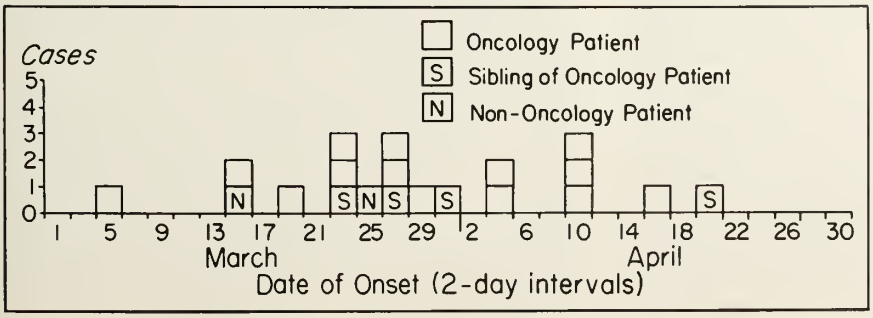

Figure 1.—Varicella among patients and family members, by date of onset, March-April 1974.

TABLE 1.—*Varicella Attack Rate Among Historically Susceptible Oncology Outpatients by Number of High-Risk Exposure Days in Clinic*

No. High-Risk Days on Which Patient Made Clinic Visit	*No. of Patients*	*No. Susceptible by History*	*Varicella Cases*	*Attack Rate Among Susceptible Patients* (Percent)*
0	34	14	0	0
1	62	33	1	3
2	20	9	2	22
≥3	22	10	3	30
TOTAL	138	66	6	9

*Progression of attack rates significant $p < .02$, $X^2 = 10.3$, 3df.

outpatient clinic on at least one high-risk day. Six cases of varicella developed among this group for an overall attack rate of 6 percent. All six cases occurred among 52 patients (12 percent) who were historically susceptible to varicella. Within this historically susceptible group, attack rates increased with increasing numbers of clinic visits on high-risk days (Table 1). No cases were observed among the 52 oncology outpatients with a history of previous varicella, nor among any of the 34 patients who attended the clinic on no high-risk days. There was no apparent relationship between underlying illness and the likelihood of varicella developing in this group of patients.

Fifty nononcology inpatients and 221 nononcology outpatients were likewise exposed on at least one day with high risk of exposure. Two cases of varicella developed in the inpatient group for an overall attack rate of 4 percent; both cases occurred among a group of 13 patients who were historically susceptible (an attack rate among susceptible patients of 15 percent). Only one case developed in the outpatient group for an overall attack rate of 0.5 percent. This particular nononcology outpatient was also the brother of an oncology patient, and had "lived in" the intermediate care facility during a high-risk period.

Use of Passive Immunization

Most of the oncology patients were passively immunized in an attempt to prevent or modify illness. A total of 35 patients received commercial pooled immunoglobulin intramuscularly in a dose of 0.4 ml per kg of body weight, whereas 14 patients received zoster immune plasma (ZIP) in doses ranging from 1.5 to 10.2 ml per kg of body weight. Although in some instances the varicella-zoster titer of the ZIP was 1:32 by complement fixation,[13] in most cases the titer of the plasma was unknown; all plasma units were negative for hepatitis-B surface antigen. Some patients received both immunoglobulin and ZIP.

Neither pooled immunoglobulin nor ZIP in these doses appeared to prevent clinical varicella. However, all four patients who received ZIP 6 to 21 days before the onset of rash had illnesses judged "atypically mild" by the attending physicians. Conversely, nine of ten patients not receiving ZIP had clinical courses considered to be "usual," or had complications of varicella (prolonged lesions, hemorrhagic varicella and fatal visceral dissemination of varicella) ($p = 0.005$ by Fisher's exact test).

Control Measures

Rigid isolation measures were not instituted until the large cluster of cases appeared in late March. Inpatients with active varicella were placed in strict isolation (private room with use of gown, gloves and mask), while exposed inpatients who were historically susceptible were placed in respiratory isolation until discharge or until 21 days had elapsed since their last exposure (usual maximum incubation period). Patients for hospital admission were carefully screened for history of previous varicella and for recent exposure to varicella. Exposed susceptible patients were placed in respiratory isolation when admitted, and segregated from unexposed susceptible patients. Whenever possible, exposed and infected patients were discharged.

In the outpatient clinic, exposed susceptible patients and patients with active varicella were seen in separate rooms. Passage between areas was limited during the period of the epidemic. The census of the intermediate care facility was purposely decreased, with as many patients being cared for in their homes or other local hospitals as possible.

Discussion

This outbreak illustrates the potential severity of varicella among immunosuppressed patients in an open therapeutic community. All cases occurred in patients who were historically susceptible to varicella, and attack rates in the outpatient setting were related to crude frequency of exposure. Uncontrolled observations suggested that passive immunization with zoster immune plasma may have modified the severity of illness. Unfortunately, strict isolation procedures were not instituted until the scope of the outbreak became

apparent at the end of March. By that time 13 of the eventual total of 20 cases had already occurred. Indeed, the cessation of this outbreak was probably due to the exposure of most susceptible patients within two incubation periods. The isolation procedures may have helped reduce the number of tertiary cases, though most cases had almost certainly been exposed by the time the control measures were instituted.

The usual distinction between inpatient, outpatient and intermediate care areas is clouded in this type of open-hospital arrangement, and the opportunities for exposure were presumably greater than in the usual hospital situation. In addition, normal siblings were also involved in the outbreak. These factors undoubtedly contributed to the high attack rate among historically susceptible oncology patients, which was 38 percent during the month of March. Nononcology patients were minimally affected; one of the two nononcology inpatients with varicella had a known community exposure while the one nononcology outpatient with varicella was almost certainly exposed in the intermediate care facility.

The value of the isolation procedures recommended in this outbreak cannot be overemphasized, however. The use of strict isolation for varicella, which is spread by the respiratory route as well as direct contact,[14] should be a routine procedure. Respiratory isolation for exposed susceptibles is also recommended because varicella has been shown to be communicable up to four days before the onset of rash, presumably by the respiratory or airborne route.[5] The most important spread of varicella in hospitals may occur before the appearance of rash and, therefore, before the diagnosis becomes obvious. Infected and exposed patients should always be discharged from the hospital when possible.

The use of prophylactic agents may be ineffective in the control of epidemic varicella though obviously not in the attenuation of illness. Although zoster immune plasma and zoster immune globulin are apparently effective in modifying varicella,[15-19] the effects on viral excretion and the period of communicability are not known; varicella may be communicable even when attenuated. In this outbreak the modification of illness by zoster immune plasma hindered appropriate control measures in one patient because of increased difficulty in diagnosing clinical varicella.

The intent of this report is to emphasize the potential danger of nosocomial varicella, especially in such an open therapeutic community. The described control measures should be instituted immediately both to reduce the spread of infection and to prevent or modify the course of illness among susceptible patients with impaired immunity.

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Skin and Soft Tissue Polymicrobial Infections From Intravenous Abuse of Drugs

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Skin and soft tissue infections were studied in 21 seriously ill narcotic addicts who had been admitted to hospital. Subcutaneous abscesses were present in 14 patients; cellulitis was noted in 3, pyomyositis in 2 and necrotizing fasciitis in 2. In four patients there was septicemia. Infections in 14 patients (66.6 percent) were associated with anaerobic bacteria, which were the exclusive isolates in 6 patients. In seven patients (33.3 percent) isolates were exclusively aerobic bacteria and in eight both aerobes and anaerobes were present. The anaerobic isolates were clostridia (six), peptostreptococci (five), bacteroides (five), peptococci (three), and one of each of Veillonella, Propionibacterium, Eubacterium, Fusobacterium and Actinomyces. Staphylococcus aureus, generally thought to be the most common cause of subcutaneous infections in addicts, was found only in four (19 percent) patients. The other aerobic isolates were Klebsiella (five) and Enterobacter (four) species. When clinical features or the Gram stain of pus suggest that anaerobic bacteria may be present, antibiotic therapy should be directed against both aerobic and anaerobic bacteria until culture results are available.

THE SYSTEMIC AND LOCAL infectious complications of narcotic addition are well known.[1] Among the more common but less well-studied are skin and soft tissue infections such as subcutaneous abscess, cellulitis, pyomyositis and necrotizing fasciitis. Hussey and Katz[2] noted skin abscess in 26 percent of 263 heroin addicts. Vollum[3] reported that 65 percent of 54 heroin addicts had a history of skin abscesses. Louria and Hensle[4] described skin abscess of cellulitis in 21 (22 percent) of 96 addicts they studied over three years. Despite the frequent occurrence of soft tissue infections in heroin addicts, relatively little is known

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about the bacteriology of such infections. Louria and Hensle[1] reported that in their series, Staphylococcus aureus was the most common pathogen. Anaerobic bacteria were rarely mentioned as causative agents of such infections; this may be because of inadequate culture techniques being employed. We have, therefore, studied skin or soft tissue infections in 21 drug addicts with careful anaerobic culture techniques.

Patients and Methods

Medical records of all drug abusers taking drugs parenterally admitted to Martin Luther King, Jr. General Hospital (Los Angeles, California) and seen by the Infectious Disease Service for consultation between July 1973 and July 1977 were reviewed. Included were all such drug abusers (taking heroin, methylphenidate hydrochloride [Ritalin], amphetamines or cocaine) who had a skin or soft tissue infection, and in whom at least one culture was drawn and the infected site cultured for aerobes and anaerobes before antibiotic therapy. Both pus and subcutaneous tissue specimens were cultured in cases of necrotizing fasciitis and pyomyositis. They were also Gram stained before culture to check to see if all morphotypes of bacteria were recovered and identified.

Bacteriology

Blood cultures were inoculated at the bedside into trypticase soy broth (Baltimore Biological Laboratories [BBL], Cockeysville, MD) and thioglycolate media (BBL) and incubated at 37°C. Pus from the infected sites was obtained either by needle aspiration or surgical drainage and placed immediately in oxygen-free containers (Anaport bottles or Anaswab Tubes, Scott Laboratories,

TABLE 1.—*Clinical Diagnosis and Culture Results in Skin and Soft Tissue Infections in 21 Drug Addicts*

Patient No.	*Anaerobic bacteria*	*Aerobic bacteria*
	SUBCUTANEOUS ABSCESS	
1	None	Serratia, Klebsiella, Enterobacter
2	Bacteroides	Group A Streptococcus
3	None	Serratia
4	Eubacterium* (pus also), Peptostreptococcus parvulus,* Propionibacterium acnes*	None
5	None	Staphylococcus aureus, Klebsiella, Enterobacter
6	Clostridium septicum, Bacteroides*	None
7	Clostridum perfringens	None
8	Clostridium perfringens	None
9	Veillonella	Staphylococcus aureus* (pus also), Alpha hemolytic Streptococcus, Neisseria
10	Bacteroides, Peptostreptococcus intermedius	Klebsiella
11	Clostridium septicum	None
12	None	Klebsiella
13	None	Group A Streptococcus
14	Actinomyces naeslundii, Bacteroides fragilis, Peptococcus variabilis, Peptostreptococcus intermedius	None
	PYOMYOSITIS	
15	None	Staphylococcus aureus
16	Peptostreptococcus intermedius	Enteroccoccus
	NECROTIZING FASCIITIS	
17	Bacteroides biacutus, Clostridium perfringens, Clostridium bifermentans, Peptostreptococcus species	Enterobacter
18	Peptococcus species	Proteus
	CELLULITIS	
19	Peptococcus magnus	Citrobacter, Enterobacter
20	Fusobacterium	Escherichia coli, Staphylococcus aureus, Klebsiella
21	None	Group A Streptococcus* (pus also)

*Positive blood cultures

Fiskeville, Rhode Island). The anaerobic cultures were processed as described in the *Anaerobe Laboratory Manual* of the Virginia Polytechnic Institute.[5] The aerobes were cultured in the conventional manner.

Therapy

All patients were treated with clindamycin and gentamicin. Concomitant surgical drainages also were done in all instances. After two days if no anaerobes were isolated, administration of clindamycin was discontinued; gentamicin therapy was stopped if the cultures failed to show aerobic Gram-negative bacilli.

Results

Types of Infection

Twenty-one patients met the criteria for inclusion into the study as shown in Table 1. Although all of them admitted to intravenous abuse of drugs, mainly of heroin, they denied "skin popping" or subcutaneous injection. All presented with skin or soft tissue infection serious enough to require admission to hospital. There were 11 women and 10 men. They were all febrile with temperatures greater than 38.3°C (101°F) and had leukocytosis. Fourteen patients had subcutaneous abscesses, three had cellulitis. Cellulitis is defined as inflammation of the skin which is tender but with no evidence of gangrene. Two patients had pyomyositis as evidenced by pus drained from the muscle substance, two patients had necrotizing fasciitis defined as rapidly spreading inflammation associated with gangrene of the skin or subcutaneous fascia (or both) but no evidence of gangrene of the muscle tissue. Soft tissue gas was shown by plain roentgenograms in three of them (cases 4, 15 and 16). In 15 of the patients foul-smelling pus was present.

Bacteriology

The culture results were as listed in Table 1. Four patients were in an extremely toxic condition as evidenced by body temperatures greater than 38.9°C (102°F), rapid thready pulse and sweating associated with leucocytosis and shift to the left and hypotension. Blood cultures were positive. In 14 patients there were anaerobic bacteria at the site of infection and, in fact, anaerobes were the only isolates in 6 patients. In the eight other patients anaerobes were found mixed with aerobic bacteria. In seven patients (33.3 percent) isolates were exclusively aerobic bacteria. Excellent correlation was noted between the Gram stain of the pus and tissue smears and the results of final culture in all patients.

Figure 1.—Note the gas bubbles in the subcutaneous tissue of the patient's arm in a case of subcutaneous abscess, due to intravenous abuse of drugs, caused by Peptostreptococcus parvulus and other bacteria (case 4, Table 1).

In all there were 48 bacterial isolates of which 24 were anaerobic and 24 aerobic. There were from one to five bacteria isolated from each patient (average 2.3). The most frequent anaerobic isolates were clostridia (including Clostridium perfringens), peptostreptococci and Bacteroides species (including one B fragilis). In addition, there were three peptococci and one each of Veillonella, Propionibacterium, Eubacterium, Fusobacterium and Actinomyces. The aerobes were as listed in Table 1. Included are Klebsiella species (four cases), and Enterobacter species (four cases), Staphylococcus aureus (four) and group A beta hemolytic streptococci in three. The following case report is provided as an example. The therapeutic efficacy of clindamycin and gentamicin in some of these cases were reported before.[6,7] Briefly, the therapeutic responses were considered satisfactory in all instances after an average duration of five days of intravenous treatment with antibiotics. There were no failures, and no difference in outcome was noted between those who were infected with anaerobic bacteria and those infected with aerobic bacteria.

Report of a Case

A 25-year-old woman, a heroin addict, was admitted because of chills and fever of two days duration associated with swelling of the upper part of the left arm. The woman (patient 4, Table 1) appeared to be in a toxic condition. Her temperature was 39.4°C (103°F). The upper left arm was notably swollen and erythematous, but no crepitations could be felt. The plain roentgenogram, however, showed soft tissue swelling and air bubbles (Figure 1). Blood cultures yielded Peptostreptococcus parvulus, Eubacterium lentum and Propionibacterium acnes (two separate sets). The laboratory values were within normal limits except that the leukocyte count was 15,900 per cu mm with a pronounced shift to the left. A deep incision was made from the lower lateral aspect of the upper arm to the shoulder, and a large volume of foul-smelling pus was drained. This pus on culture grew Eubacterium lentum. The patient was treated with clindamycin and gentamicin for seven days and recovery was uneventful.

Discussion

Skin and soft tissue infections in heroin addicts are generally thought to be caused by Staphylococcus aureus.[4,8] Lerner and co-workers, for instance, found that all but one of the eight skin abscesses they cultured were caused by S. aureus.[9] Only one patient in their study had a Bacteroides infection of the neck. Necrotizing fasciitis and pyomyositis in drug addicts have been reported to be caused by both aerobic and anaerobic bacteria.[10,11]

Lewis and Gorbach,[11] utilizing proper anaerobic culture techniques, reported that these infections were associated with Staphylococcus aureus, streptococci and peptostreptococci and other anaerobes. As shown in our study, nearly two thirds of the heroin addicts' skin and soft tissue infections were caused by anaerobic bacteria. In fact, in six patients (28 percent) there were pure anaerobic infections.

Anaerobic infection of soft tissue may be suggested by radiological evidence of free air bubbles or air in the fascial planes and the characteristic foul smell produced by anaerobes. These signs are not always present in anaerobic infections; furthermore, they can be misleadingly present in exclusive aerobic infections as well. In our study only three patients had radiologically shown free air bubbles in the tissues; in several there was no foul odor. Roentgenographic evidence of free air and foul odor when present strongly suggest anaerobic infection.

The Gram stain is a simple technique that can be extremely valuable in the diagnosis of anaerobic infections. The presence of multiple morphological types of bacteria in Gram stains of pus is characteristic of anaerobic infection. In contrast, most aerobic infections, such as those caused by S. aureus or Pseudomonas are of a singular morphotype showing either Gram-positive cocci or Gram-negative bacilli, as the case may be. The presence of both cocci and bacilli together in the same Gram-stained smear should suggest anaerobic infection or mixed aerobic-anaerobic infection. In our study excellent correlation was noted between Gram stains and final culture results; all morphotypes of bacteria seen on Gram stain were accounted for by culture results. The Gram stain features, soft tissue gas and foul smell, if all present together, make the diagnosis of anaerobic infection very likely. If careful anaerobic culture techniques are utilized in processing specimens taken from such patients, the diagnosis can be confirmed.

Most of the patients in our study were heroin addicts. Methylphenidate abuse as reported by Brooks and associates[12] was associated with soft tissue infections due to Eikenella corrodens, an aerobic Gram-negative rod resistant to clindamycin. They reported that anaerobic bacteria were infrequently associated with E. corrodens infections. Apparently abuse of different substances may predispose to different types of infections.

In contrast to findings in previous studies of skin and soft tissue infections in drug addicts the overall incidence of S. aureus in our study was only 19 percent; only four of 21 patients were infected with this organism. A recent study[13] of cutaneous abscesses in nonaddicts found S. aureus in only 24 percent. Anaerobes were frequently isolated from the remainder. The patients were all well enough to be treated as outpatients. These results were similar to ours, although our study involved only seriously ill patients who had been admitted to hospital. There was no correlation between a specific diagnostic category and the microbiologic findings in our study. However, precise understanding of the microbiology of severe skin and soft tissue lesions in drug addicts is of obvious importance to select optimum therapy. Although surgical drainage is imperative, concomitant antibiotic therapy is needed to allay

systemic toxicity and hasten recovery. When features such as soft tissue gas or foul smell are present, or when the Gram stain of pus shows different morphotypes of bacteria, antibiotic therapy should be directed against anaerobic as well as aerobic bacteria until the culture results are available. Pus from all such lesions should be cultured using proper anaerobic techniques.

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Overlooked Causes of an Ischemic Leg

ONE SOMETIMES OVERLOOKED cause of an ischemic leg is a diabetic person with a neuropathy who grinds a hole into the skin of his foot and infection develops, superimposed on that. He may have perfectly good pulses and perfectly good arterial supply. Infection develops superimposed on this kind of trauma and then ischemia and gangrene develop, indeed secondary to the infection. This is a variant and a peculiar one. This lends itself to radical debridement, just as one would a carbuncle. Sometimes, one does the radical debridement because the same type of necrotizing infection will occur in the presence of occluded arteries. And this is what one gets when one has occluded arteries—gets a necrotizing infection, clears it out in order to control the infection and then ischemia takes over.

—ANTHONY M. IMPARATO, MD, *New York City*

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Medical Progress

Strokes, Transient Ischemic Attacks and Asymptomatic Bruits

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Research into noninvasive techniques for evaluating cerebrovascular insufficiency has shown that hemodynamically significant lesions can be identified with considerable accuracy. Concurrently, recent descriptions of carefully applied medical and surgical therapy indicate that thromboembolic stroke can be effectively prevented when patients are allocated to the proper therapeutic protocols. The approach of these two lines of basic investigation to the clinical focal point of stroke control make it imperative that clinicians review the tools at hand for identifying persons at high risk, as well as the available therapeutic alternatives for effective stroke prevention.

THE POSITION OF STROKES as one of the major public health problems facing Western civilization is based on a foundation of awesome statistics. There are more than 400,000 new cases of stroke in the United States every year, and about 40 percent of the persons so afflicted will die within 30 days. Moreover, half of the survivors will be totally disabled. In 1972 the annual cost to the country was estimated at 6.2 billion dollars.[1,2]

In Europe there are more than 1 million new cases of stroke each year, with a 30 percent mortality as well as a 60 percent incidence of substantial disability among the survivors. In fact, only 30 percent of the survivors ever return to gainful employment. The World Health Organization has estimated that there are 1 million persons in Europe permanently disabled by a stroke, with initial hospital care costing 7 billion dollars and follow-up institutional care costing 500 million dollars a year.[3,4]

Success in addressing this problem depends on a virtual revolution in our thinking about stroke. Cerebral stroke is in many ways analogous to a solar eclipse—a seemingly capricious and unheralded event only to the uninitiated. Although certainly not predictable with astronomical accuracy, the inexorable progress of the atherosclerotic plaque is accompanied by a constellation of evolving signs and symptoms which offer an astute clinician many opportunities to intercede, and in contradistinction to a solar eclipse, prevent the final statistically predictable event. Indeed, it is crucial that clinicians not view stroke as an isolated entity, or according to the anachronistic description of "cerebral vascular accident," but as one stage of disease progression in an orderly, discernible, evolutionary process ranging from the first appearance of the atherosclerotic plaque through its early clinical manifestations such as asymptomatic cervical bruits, attacks of transient cerebral ischemia and then, finally, to the fixed neurologic deficit of the completed stroke.

Although strokes are the result of a somewhat diverse group of etiologic diseases manifested by a rather sudden, and for the most part irreversible, central neurologic deficit, most occur as a consequence of progressive atherosclerotic disease. Of the entire population of patients admitted to a hospital with a diagnosis of stroke, the condition in approximately 60 percent to 70 percent of cases stems from infarction due to thromboembolism, and in 20 percent from intracerebral hemorrhage.[4] In 5,184 men and women entered into the Framingham study over 18 years, 78

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percent of the strokes that occurred were attributable to thromboembolic disease, and of these approximately 2 percent had a known cardiac origin. Subarachnoid hemorrhage preceded the stroke in 12 percent of the patients, and intracerebral hemorrhage afflicted an additional 5 percent before the stroke. Moreover, 5 percent of the strokes were attributable to various less common illnesses.[5]

In 1919 Hunt suggested the relationship between stroke and occlusive disease in the extracranial cerebrovascular system.[6] Subsequent epidemiologic studies substantiated these initial impressions, ascribing approximately 60 percent of all strokes to disease in the carotid and vertebral vessels. Recognition and control of disease in this region constitute the particular focus of this review.

It must be appreciated at the outset that effective therapy of stroke depends on early recognition and prophylaxis. This caveat is readily ascertained from the medical literature.[7,8] Despite two decades of effort at establishing effective therapeutic measures once a stroke has occurred, progress remains elusive. Consequently, the mortality has not been altered during this period of various treatment regimens.[7-9] The natural history and course of stroke have likewise remained refractory to almost every therapeutic protocol. When hemiplegia persists for 36 hours or more, the possibility of permanent incapacitating deficit is greater than 90 percent. At the end of seven days about 40 percent of the surviving patients will be neurologically stable, with another 35 percent of patients experiencing continuing neurologic improvement.[4,7]

To reduce the dimensions of this awesome problem, the first step is to recognize the population at risk. These persons can be identified by many of the stigmata of atherosclerotic disease. Although it has not been clearly established whether these distinguishing characteristics represent true risk factors or merely coincidental associated phenomena, they serve as useful markers; their control produces well-documented salutary effects, even though the precise role in stroke prevention has not been positively identified.[8,10-12] Each risk factor will roughly double the incidence of stroke for a similar-age but unafflicted cohort in the general population,[4] the most noteworthy being arterial hypertension as evidenced by more than 160/90 mm of mercury pressure. In the Framingham study, however, hypertensive patients had a fourfold increase in stroke incidence over the normotensive population.[5] Radiological evidence of cardiomegaly or electrocardiographic indication of left ventricular hypertrophy or of coronary artery disease will double the incidence of stroke, as will the presence of congestive heart failure, cardiac arrhythmia or atrial fibrillation. Abnormal glucose tolerance test results, manifested by a two-hour postprandial sugar determination higher than 160 mg per dl or a fasting blood sugar greater than 120 mg per dl, are also indicators. While control of these abnormalities has become axiomatic in modern medicine, it should be appreciated that the effect of control on stroke incidence has yet to be proven.[11] There is evidence, however, that control of these risk factors serves to decelerate the atherosclerotic process, and one would intuitively anticipate a coincidental effect on the carotid atherosclerotic occlusive process. In addition, such factors as smoking, hyperlipidemia, diabetes, use of oral contraceptives and stress all lead to increased platelet aggregability which, as will be pointed out, are specifically pertinent to the occurrence of stroke. When any of these stigmata are encountered in a patient without symptoms of cerebrovascular disease, particular emphasis should be focused on identifying an occult carotid lesion that may be interfering with cerebrovascular hemodynamics. Moreover, it is important to realize that extracranial cerebrovascular disease can progress up to and include total occlusion of the internal carotid artery without symptomatic manifestations, until stroke occurs, seemingly without premonitory warning. Although atherosclerosis is appropriately considered a generalized disease process, there are almost invariably specific sites of predilection for stenotic lesions which give rise to the varied symptom complexes.

Physical examination of every patient in the high-risk group for stroke must give attention to the cervical pulses and include a notation as to the presence or absence of cervical bruits.

Cervical Pulses

Reduction in palpable pulse is a hallmark of atherosclerotic occlusive disease in the carotid system, and may often precede symptoms of cerebrovascular insufficiency. Measurement of blood pressure in both brachial arteries and palpation of both common carotid arteries provide valuable information about the integrity of the origin of the great vessels arising from the aortic

arch. Symmetrical blood pressure in the brachial arteries with a weak right carotid pulse generally indicates a lesion at the right common carotid origin. A weak right carotid pulse associated with an ipsilateral reduction in brachial artery pressure signifies a lesion in the innominate artery. Conversely, a reduced right brachial artery pressure with a normal right carotid pulse may serve to attribute a loud asymptomatic bruit in the neck to a subclavian lesion, with no concomitant extracranial cerebrovascular disease. Palpation of the superficial temporal artery pulses is likewise useful and a prominent enlarged superficial temporal artery is often associated with an occluded ipsilateral internal carotid artery, since the superficial temporal artery is a common collateral channel.[13,14]

Although the enlargement of collateral vessels as a consequence of atherosclerotic occlusive disease is generally a reliable indicator of vascular occlusive pathologic conditions, a weak superficial temporal artery pulse may help to identify a lesion at the carotid bifurcation and explain a perplexing cervical bruit. Of lesions that occur in the carotid artery system, 5 percent will be identified by angiography at the aortic arch origin of the common carotid artery and 90 percent will be located at the common carotid artery bifurcation in the neck; another 5 percent will be found in that portion of the intracranial carotid artery referred to as the siphon. Surprisingly minor atherosclerotic disease is encountered elsewhere along the carotid system, even in the face of advanced occlusive lesions. Palpation of an abnormal pulse should alert clinicians to the need for further investigation.

Auscultation

Few findings on routine physical examination cause more consternation than the asymptomatic carotid bruit, yet it is a finding of consummate importance. Much has been written concerning the inaccuracy of interpreting the anatomic site or meaning of the asymptomatic cervical bruit, but a few careful maneuvers help immeasurably to evaluate these abnormal sounds correctly.[15] The exercise would be only academic, however, were it not for the clinical value of recognizing this physical finding. By stepwise auscultation, the origin of a bruit can be reliably surmised. Although it would be difficult to ascribe a bruit at the angle of the jaw to internal carotid versus external carotid arteries, identification of those bruits transmitted from the aortic arch, or arising from the vertebral or subclavian arteries, should not prove insurmountable. Numerous attempts have been made to correlate the cervical bruit with subsequent angiographic findings, and while significant stenotic lesions can be found angiographically in 50 percent of patients with cervical bruits, conversely it has been reported that approximately 20 percent of angiographically observed stenotic lesions were not associated with cervical bruits.[15] Nevertheless, the recognition of a bruit is imperative, and in my experience it is unlikely that a carotid bruit can be heard without substantial pathology being identified angiographically. I am convinced that a careful clinician can distinguish bruits with far better accuracy than that reported in the medical literature, particularly when the investigator's objective was to prove the superiority of some other modality of assessment. Bruits evolve concomitantly with their plaques: from the soft, low-pitched, short-duration bruit of the moderate stenosis, to the loud, rough, prolonged systolic bruit of the 70 percent to 80 percent stenosis, to the higher-pitched, ever softer, though protracted bruits lasting into diastole, with an 80 percent to 90 percent stenosis. Finally they become barely audible and then silent as the stenosis increases beyond 95 percent.

A bruit is foreign to the neck, and when it is heard there, its origin must be clarified. "Walking" the stethoscope up the neck is the most useful way of separating the aortic outflow murmurs from carotid bruits. The carotid bifurcation bruit, which is by far the most important, increases in intensity as the angle of the mandible is approached. Bruits heard lateral to the sternocleidomastoid muscle at the root of the neck are usually subclavian or vertebral in origin.

The significance of asymptomatic bruits has been clarified by recent epidemiologic data. In studies where careful attention has been directed towards identifying bruits of cervical and, most noteworthy, carotid origin, angiographic evaluation has shown that 90 percent of asymptomatic bruits auscultated at the carotid bifurcation arise from the internal carotid artery and 10 percent from the external carotid artery. In one group of 59 patients with asymptomatic cervical bruits followed for up to eight years, 51 percent remained asymptomatic, whereas in 25 percent transient ischemic attacks occurred and in 24 percent there were frank strokes. Eleven patients went on to total internal carotid artery occlusion and in four

among them the bruits disappeared when occlusion occurred.[16]

Most of the patients in whom stroke developed did not have antecedent transient ischemic attacks. As a group, then, 49 percent of the patients with asymptomatic carotid bruits had either transient ischemic attacks or frank strokes during a rather brief follow-up period. Epidemiologic studies such as this have indicated the considerable significance and stroke risk that accompany an asymptomatic carotid bruit,[16,17] but few studies have been done on the chronologic progression of cervical bruits or on the precise temporal evolution of an atherosclerotic carotid plaque. One study, however, in which cases were followed by serial angiograms, found that in 38 percent of the patients there was no demonstrable change in the size of the carotid atheromata, but in 12 percent there was a gradual increase in size; moreover, in 35 percent of the lesions, the stenosis increased at a rate faster than 25 percent per year.[18,19]

Debate continues on the meaning and accuracy of asymptomatic cervical bruits, but no clinical data have been generated. If a bruit is not heard, nothing can be done about it; aside from recognizing that occasionally substantial arterial disease can exist in the absence of a bruit, agonizing over it will not help. Because cerebrovascular insufficiency is marked by other indicators, the absence of a bruit where it might be anticipated is interesting but minimally important. If a bruit is present, however, it represents an abnormal physical finding that requires further elucidation. Within this cohort of patients, there are many in whom a stroke eventually occurs, and in a considerable number of these there will be a sudden stroke without premonitory warning.[16] Inherent variation in the accuracy of clinical examination, together with the multiplicity of innocuous sources of cervical bruits added to the potential morbidity from aortic arch angiography, does not in my opinion justify routine angiography in cases of asymptomatic cervical bruits. Fortunately, noninvasive tests that are accurate, safe and moderate in cost enable clinicians to readily identify a hemodynamically significant carotid lesion as a source of the cervical bruit. These tests should be used in every case of an asymptomatic cervical bruit or an abnormal cervical pulse. If these tests are negative, reassessment should be done in the patient at yearly intervals to ascertain possible progression of a nonocclusive carotid lesion. On the other hand, if the test findings indicate a lesion of hemodynamic significance in the carotid artery system, then arteriography should be done in the patient, even though no symptoms are present. If the noninvasive test findings are positive, there is a 95 percent chance that hemodynamically significant lesions will be identified in the internal carotid artery system.

Noninvasive Cerebrovascular Tests

Although many promising tests have surfaced only to be later rejected, several simple, safe, reliable tests have gained wide acceptance over a

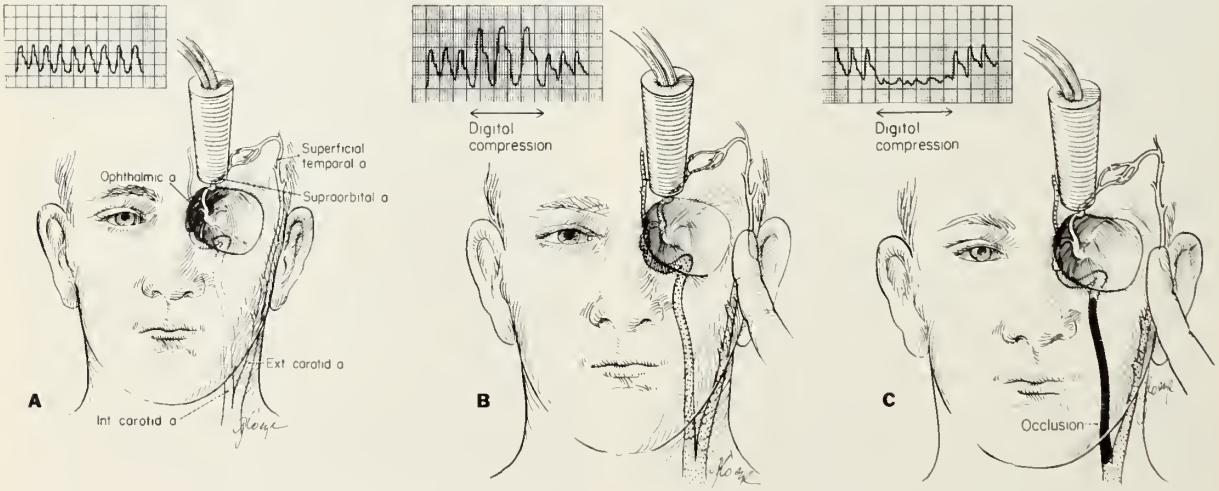

Figure 1.—A, Doppler flow meter evaluation of the supraorbital artery in the Doppler ophthalmic test; note the normal wave tracing. **B,** With normal internal carotid artery flow, *augmentation* is seen on the Doppler tracing of the supraorbital artery with digital compression of the superficial temporal artery. **C,** In the presence of hemodynamically significant stenosis, or occlusion of the internal carotid artery, the Doppler flow tracing shows obliteration of flow in the supraorbital artery upon digital compression of the superficial temporal artery.

Figure 2.—Doppler ophthalmic test being carried out.

period of time. With wide clinical application has come validation, not only under the scrutiny of investigative laboratories but also under the rigors of clinical use. Two tests that have earned the widest application and validation in the medical literature are the Doppler ophthalmic test and oculopneumoplethysmography.[20] The Doppler ophthalmic test has been used in our laboratory since 1970.[21,22] The method and clinical application have been well-documented by us as well as by other investigators.[23,24] This simple procedure depends on the identification of a prominent and fairly consistent collateral arterial pathway between the external carotid artery and a hemodynamically compromised internal carotid artery (Figure 1). A small ultrasound flow probe identifies the supraorbital artery, and the changes in its flow characteristics are noted subsequent to digital occlusion of the superficial temporal artery (Figure 2). Normally, supraorbital artery flow will increase after this maneuver. With internal carotid artery occlusive disease, however, flow is reduced to a pronounced degree or absent. The test is noted as being either positive (an abnormal flow response) or negative (normal flow response).

The oculopneumoplethysmography test described by Gee and co-workers directly records the ophthalmic artery pulse from which ophthalmic artery blood pressure can be ascertained by an analogue method.[25-27] Two hemispheric paralimbal suction cups are connected to the patient's eyes and to separate transducers by means of flexible tubing (Figure 3). By using a vacuum pump, a negative pressure of 300 mm of mercury is applied which serves to adhere the cups to the sclerae. The vacuum is then reduced to atmospheric pressure in a linear fashion over 25 seconds. The

Figure 3.—Oculopneumoplethysmography test being done.

pulse pressure alterations are superimposed on this calibrated pressure range, transmitted to the transducers, and then visualized on a strip chart recorder tracing, creating a pressure-dependent deflection for each eye. At a vacuum pressure of 300 mm of mercury, a deflection recorded from the transducer corresponds to an internal carotid artery pressure of 110 mm of mercury[28] (Figure 4). Ophthalmic artery pressures assessed by the Gee oculopneumoplethysmography method average 70 percent of the simultaneously recorded brachial artery pressure with a range of 60 percent to 95 percent. Criteria have been established for interpreting the results of this test that achieve a 97 percent accuracy in identifying a hemodynamically significant lesion in the internal carotid artery system. When these tests show an abnormality in flow or pressure, the accuracy is such that it can be assumed that a lesion of hemodynamic significance exists in the internal carotid artery system. Angiography should be undertaken, and if the angiogram confirms the diagnosis and further shows that the lesion is amenable to surgical correction, this modality of therapy should be seriously considered, for we have now shown a smaller subgroup of the "asymptomatic bruit" population—that is, those with an asymptomatic hemodynamically significant lesion. Although never studied in great detail, intuitively it can be assumed that we are dealing here with patients who are at highest risk of sudden stroke (Figure 5).

Transient Ischemic Attacks

Transient ischemic attacks or little strokes occur frequently among older persons, generally carrying a dire prognosis[29-31] (Figure 6). Because the symptoms are usually quite characteristic, they tend to be readily diagnosed.[32] Amaurosis fugax—or painless, transient, monocular blind-

ness—is a typical symptom, often described as a "shade coming down over one eye" or a "shutter closing," first graying the vision, then leading to total blindness, after which vision usually returns within 30 to 60 seconds. This symptom is one of the pathognomonic indicators of carotid artery disease.[33] A variable number of persons in this group will experience recurrent attacks and then progress to complete monocular blindness with retinal ischemia and infarction. The incidence of subsequent cerebral hemispheric stroke is about the same in this type of symptom complex as for other types of transient ischemic attacks. In a study of 70 such patients, 96 percent of the angiograms indicated atherosclerotic lesions at the appropriate carotid bifurcation.[33] In a similar age group, asymptomatic irregularity at the carotid bifurcation could be expected in about 25 percent of patients.[33] Episodes of transient ischemia are usually manifestations of an ulcerating, embolizing atherosclerotic plaque. Although attacks of retinal ischemia have been attributed to a known cardiac embolic source in 10 percent to 12 percent of cases, focal cerebral ischemia is uncommon from a cardiac source.

In addition to amaurosis fugax, a wide spectrum of transient neurologic dysfunctions develop, referred to as TIA's (transient ischemia attacks). Among the most typical are unilateral weakness, paresthesias or sensory loss, usually lasting a few minutes but occasionally persisting up to 24 hours and involving either the arm or the leg. Intermittent difficulty in speech or written communication as well as intermittent severe ataxia or severe episodic double vision are also frequent manifestations of transient cerebral ischemia. Episodic dimness of vision or bilateral loss of vision with recovery over 2 to 30 minutes is often reported.

Occasionally the syndrome resembles the distribution of a specific arterial supply. These should be recognized even though the anatomic site of a lesion cannot be predicted on the basis of the symptom complex. Through the years this disquieting observation has caused considerable confusion. Middle cerebral artery symptoms tend to result in a hemiplegia, hemihypesthesia, hemianesthesia, or homonymous hemianopia. Aphasia, dysphasia, and hemiparesis also signify middle cerebral artery transient ischemia attacks. Anterior cerebral artery symptoms usually present as weakness of the lower extremity (but not of the upper extremity). Mental changes may range from mild to frank dementia, dyspraxia and apraxia. Vertebrobasilar symptoms typically accompany abnormalities of motor function such as weakness, clumsiness or paralysis of one or more extremities up to and including quadriplegia. Vertigo, nystagmus, and bilateral sensory or motor loss associated with palsies of cranial nerves three to nine are also indicative of vertebrobasilar insufficiency. In addition, bilateral homonymous hemianopia, ataxia, imbalance, unsteadiness and disequilibrium are frequently seen in attacks of vertebrobasilar insufficiency.

Although the symptoms may be typical of a particular arterial distribution, it should be reiterated that anatomical localization on the basis of symptom complex alone is apt to be misleading. In one cooperative study, 57 percent of the patients thought definitely to have vertebrobasilar

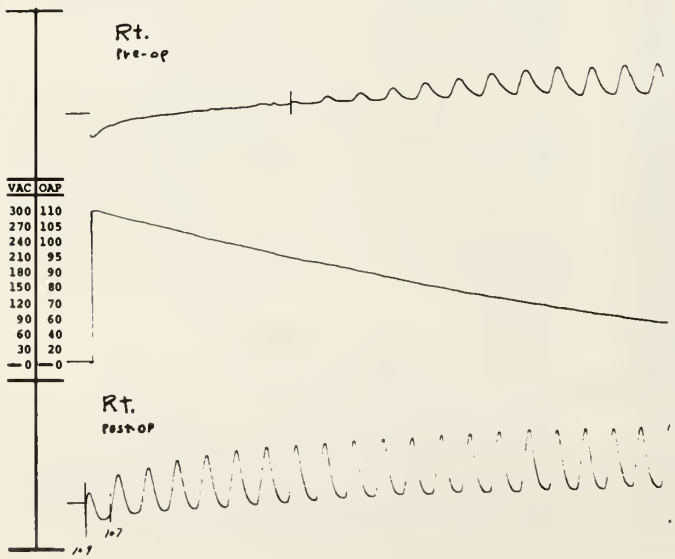

Figure 4.—Oculopneumoplethysmographic wave tracing on a 57-year-old patient showing **(above)** a hemodynamically significant lesion in the right internal carotid artery that caused recurrent attacks of transient left hemiparesis, and **(below)** a normal wave pattern after internal carotid endarterectomy, which was followed by relief of symptoms. The sloping line between the two tracings indicates the decline in vacuum in the scleral cups. The point on the slope at which the pressure wave first appears can be used to calculate the ophthalmic artery pressure by use of the analogue ruler on the left-hand side of the tracing.

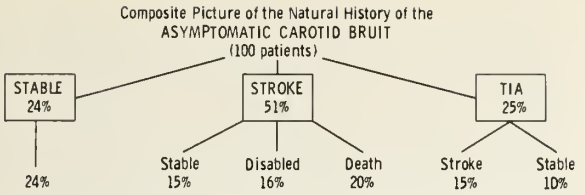

Figure 5.—Probable outcome of an asymptomatic carotid bruit (composite picture from several epidemiologic studies).

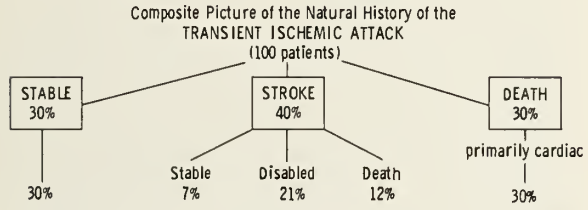

Figure 6.—Probable natural history of a cerebral transient ischemic attack.

transient ischemic attacks were angiographically shown to have only unilateral or bilateral carotid lesions.[15] In the evolution of the atherosclerotic lesion, one or more of various collateral pathways may develop. The ischemic symptoms may occur in the anatomic site closest to the lesion, or farthest from the lesion if stenosis develops in the collateral artery supplying the distribution of an occluded vessel.

Several other important clinical features of transient ischemic attacks become evident through epidemiologic studies. An aspect of transient ischemic attacks which has proven to be equally as disconcerting as the problem of anatomical localization is the inability to ascribe the symptom complex to a specific type of occlusive lesion. An ulcerated, embolizing, but nonobstructing plaque, a stenotic hemodynamically significant plaque and a totally occluded internal carotid artery may all present with the same symptom complex.[34] We have observed patients evolve through documented ulcerated plaque embolization, stenosis and then occlusion without change in the characteristics of the TIA.[22] About 25 percent of patients with carotid transient ischemic attacks will have a totally occluded vessel on the appropriate side at the time of initial investigation. Patients in whom a total occlusion of the carotid artery develops during the period of observation will have a 33 percent chance of continuing to have transient ischemic attacks in the same distribution.

One fact, however, remains fairly consistent: when any of the symptom complexes are encountered, there is a high probability that a lesion will be found in the extracranial cerebrovascular system. Although, as previously noted, attacks of retinal ischemia have been attributed to a known cardiac source of emboli (in 10 percent to 12 percent of the cases), focal cerebral ischemia is uncommon from cardiac embolization and extremely uncommon in cardiac dysrhythmia.[35] Episodes of cardiac dysrhythmia are far more likely to result in transient episodes of dizziness or syncopy than the focal characteristics of carotid embolization.[36]

Unquestionably, the natural history and the implication for development of stroke are the most important issues in dealing with a patient having transient ischemic attacks. The attacks per se usually prove to be inconsequential, and information about them often can be elicited in history-taking when a patient presents with a completely unrelated problem.[18,19,29]

A number of epidemiologic studies have shed light on the fate of patients with attacks of transient cerebral ischemia, and although they vary, depending on the type of population surveyed and the associated risk factors encompassed by that population, a fairly consistent pattern is readily discernible. In one study, for example, more than 60 percent of patients with transient ischemic attacks progressed to a completed stroke within a mean period of 4.6 years.[4,31] In a multicenter study reported by Fields, strokes occurred in 18 percent of the patients within the four-year observation period.[37] Two other important risk indicators were identified. First, in patients over 65 years of age, 50 percent went on to stroke or further episodes of transient cerebral ischemia during this short follow-up period. Second, in patients who had a single transient ischemic attack there was a 14 percent incidence of subsequent stroke, whereas those with multiple transient ischemic attacks had a 45 percent incidence of stroke within the same observation period.[37] In one of the most carefully controlled epidemiologic studies, encompassing a relatively stable population in Minnesota that was followed over a 20-year period,[38] frank hemiplegic stroke occurred in 36 percent of the patients during the period of observation. In 51 percent of these patients the neurologic event occurred in the first year, and in 21 percent during the first month. This represented more than 15 times the anticipated stroke occurrence in an age-matched population.

That a person with a transient ischemic attack

is at high risk for stroke seems beyond question.[17,39] An evaluation of such a patient is predicated on the need to establish the diagnosis beyond reasonable doubt and establish the location of the lesion anatomically. If, as in most instances, the lesion is situated at the carotid bifurcation, it is important to establish whether the lesion is a nonobstructing but embolizing plaque, or an obstructing, hemodynamically significant lesion. Examination of the carotid pulses and auscultation for bruits are essential, inasmuch as the site of origin of the transient ischemic attack and the bruit correlate in 60 percent of the cases.[40] Noninvasive pressure and flow tests of cerebrovascular function are useful in localizing the lesion, helping to interpret the angiogram when multiple lesions are present, and enabling a follow-up evaluation of the patients whether they are treated medically or surgically. If the noninvasive studies do not indicate a hemodynamically obstructing lesion, it is likely that an embolizing plaque is present and the patient may benefit from antiplatelet therapy. Although determining the precise anatomic location is not necessary for effective antiplatelet therapy, it has been our practice to advise angiographic investigation in all patients with transient ischemic attacks in order to ascertain the status of the cerebral vascular circulation before instituting either medical or surgical therapy.

Concomitant with the evolution of diagnostic tests to assess the prestroke lesions more accurately has come the development of new, highly effective prophylactic medical regimens.

Medical Therapy

Medical therapy has a long history encompassing carefully controlled clinical trials and sporadic reports of anecdotal experience.[41-45] The benefits of reducing hypertension, decreasing hyperlipidemia, and controlling diabetes with diet or insulin are manifold; reduction in stroke risk is only one of the benefits. Anticoagulant therapy has undergone considerable trial, and although it has achieved great benefit in protection from embolization of cardiac origin, valvular disease, atrial fibrillation and prosthetic valves, there has been no success in treating thromboembolic stroke from other causes. Moreover, significant morbidity and mortality have ensued as a result of hemorrhagic complications.[42,45,46] The recognition that embolization of platelet aggregates represents the prevailing cause of transient ischemic attacks and stroke has focused attention on the possibilities of antiplatelet therapy.[47-52] Platelet aggregates form the chief thromboembolic material in the arterial circulation and have been shown in the cerebral circulation subsequent to TIA and stroke, as well as in the retinal circulation following episodes of amaurosis fugax.[34,51-54] In atherosclerotic disease of the extracranial cerebrovascular system, ulcerations of the diseased intima can frequently be shown, particularly in areas of turbulence such as the carotid bifurcations.[55] At the time of operation in cases of recurrent transient cerebral ischemia attacks, these ulcerations have been seen to contain fresh clumps of platelet aggregates.[51,55] Even in occlusive lesions, ulcerations can be seen distal to the stenosis where the jet of blood strikes the intima, and normal laminar flow is disorganized. It is likely that even in stenotic hemodynamically significant lesions many episodes of transient cerebral ischemia are secondary to embolization rather than to transient interruption of cerebral perfusion.

When intimal ulceration develops, collagen fibers of the arterial media are exposed. Collagen is a potent platelet aggregating agent, both *in vivo* and *in vitro*. Platelets coming in contact with exposed collagen undergo a change in the cell surface membrane which causes the platelets to adhere to the collagen substrate and leads to platelet degranulation, releasing platelet factors into the surrounding blood. This "release reaction" of the platelets is followed by further platelet aggregation and augmentation of the release reaction, much as the cascade effect of blood coagulation accelerates thrombosis in the venous circulation. Although the platelet aggregate is stabilized by fibrin, the shear forces of the blood are such that fragmentation and embolization are characteristic sequelae; with the cycle of embolization, exposure of collagen, reaggregation of platelets and then reembolization forming a typical clinical cycle. As platelet aggregation and release take place, the granules release vasoactive amines and other coagulation substrates into the surrounding blood. Prostaglandin biosynthesis is initiated, and this results in the synthesis of thromboxane A_2 which is both a potent aggregating agent and the strongest naturally occurring vasoconstricting amine. Although quite labile, with a half-life of 32 seconds, this factor is probably most important in generating a transient ischemic attack when the area of transient ischemia (such as the middle cerebral artery distribution) tends to be out of

proportion to the probable size of the embolizing aggregates, and indeed, angiographic evidence of major vascular obstruction is rarely obtained.

The effect of thromboxane A_2 on the cerebrovascular system has been well shown, and although it is an effective constrictor of both coronary and renal arteries, its effect is greatly augmented on cerebral vessels. For example, thromboxane A_2 has been shown to be at least ten times more powerful than 5-hydroxy-tryptamine or PGF_2 alpha on the cerebral vessels. Under experimental conditions, thromboxane B_2, the metabolic product of thromboxane A_2, is found in large quantities in brain tissue after vasospastic episodes, suggesting that thromboxane A_2 may also be produced intracerebrally.[56]

The biochemical reactions involved in this process have been carefully documented[47,57-59] (Figure 7). When platelets come in contact with collagen, phospholipids in the platelet membrane are acted upon by phospholipase, producing arachidonic acid. The reaction of arachidonic acid to the cyclic endoperoxides, PGG_2 and PGH_2 is mediated by a cyclooxygenase, prostaglandin synthetase. The cyclic endoperoxides are further metabolized to thromboxane A_2, and thence to the stable end-product, thromboxane B_2. The endoperoxides also proceed to form PGE_2, PGF_2 alpha, and PGD_2.[59] Review of these metabolic pathways is critical to understanding the appropriate medical therapy and the action of various drug protocols. Of the known pharmacologic agents that affect platelet function, acetylsalicylic acid, dipyridamole and sulfinpyrazone have been given extensive clinical trials.[12,43,47-52,57,58,60] Aspirin has a specific effect on the platelet because it acts to acetylate the cyclooxygenase which mediates the conversion of arachidonic acid to the cyclic endoperoxides which are the prostaglandin precursors. Once a platelet's membrane cyclooxygenase is acetylated, the platelet ceases to function normally for the duration of its circulatory life. The reaction is irreversible, and it is therefore possible with one dose of aspirin to acetylate the cyloxygenase of all of the circulating platelets, which have an average life span of ten days. Platelet function will then return to normal at the rate of 10 percent each day. In an average patient, a dose of 10 grains of aspirin will effect this acetylation, although there is some variability that can best be assessed by platelet function tests such as collagen and epinephrine-stimulated aggregation.[47] Sulfinpyrazone is a reversible, competitive inhibitor of cyclooxygenase activity and its effects can be overcome by strong aggregating stimuli which can then generate high concentrations of arachidonic acid. The effect of dipyridamole is to raise cyclic adenosine monophosphate stabilizing the

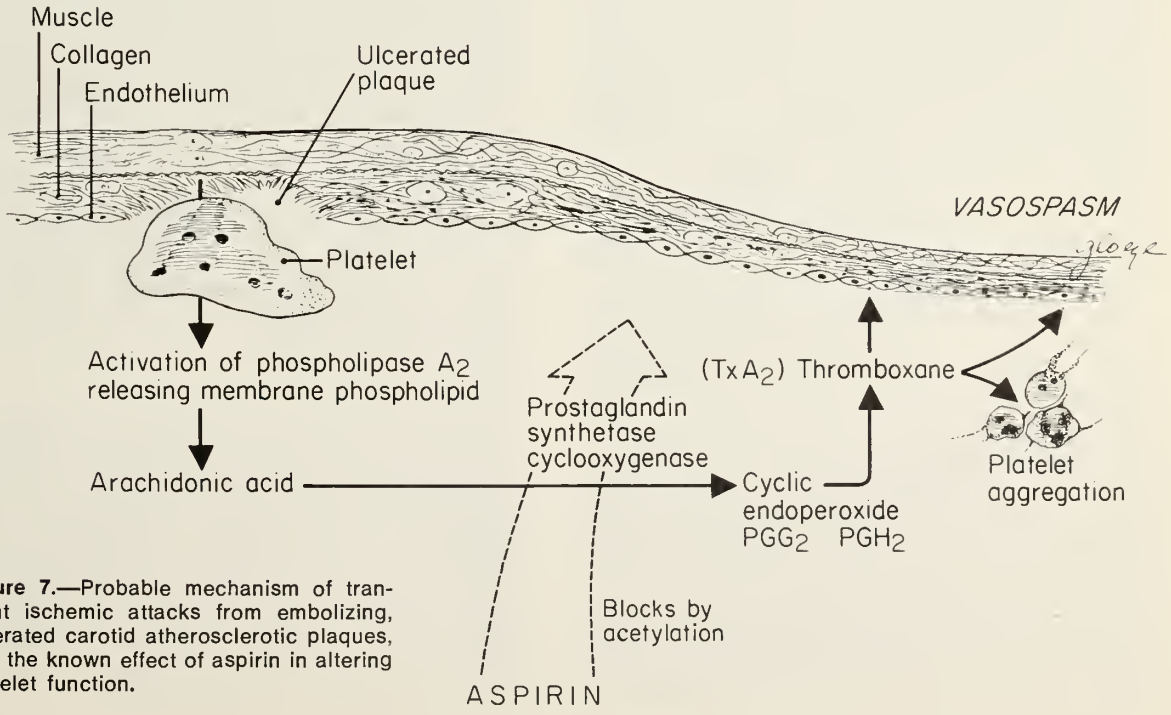

Figure 7.—Probable mechanism of transient ischemic attacks from embolizing, ulcerated carotid atherosclerotic plaques, and the known effect of aspirin in altering platelet function.

platelet membrane, and interfering with platelet aggregation and the release reaction. The effect of dipyridamole lasts a maximum of four to six hours, after which platelet function returns to normal.

Early reports of the United States Multicenter studies on the effects of aspirin on cerebral ischemia are now available for analysis.[48,61] When the endpoints of stroke or death were considered, there was unfortunately no significant difference between the groups that took aspirin and the group that had the placebo. If certain subgroups are separated out, however, important information regarding the therapy of transient ischemic attacks may be obtained. There was substantial protection from stroke and death if the groups were subdivided into those that had an "appropriate" lesion compared to those who had an "inappropriate" lesion. When an ulcerated plaque occurred in the vessel supplying the symptomatic hemisphere, there was a 13.8 percent incidence of stroke or death in the aspirin-treated group compared with a 43.1 percent incidence of stroke or death in the group taking the placebo, a statistically significant difference. If the lesion was inappropriate—for example, carotid occlusion where embolization is unlikely—there was a 35 percent incidence of stroke or death in the aspirin-treated group compared with a 47 percent incidence of stroke or death in the group receiving placebo, a difference having no statistical significance. The authors pointed out that when the patients were retrospectively stratified into groups with carotid lesions appropriate to the presenting symptoms and groups having no appropriate anatomic lesion or complete occlusion of the appropriate artery, significant differences can be found. Where lesions appropriate to the presenting symptoms were identified, there was a statistically significant reduction in the incidence of death, nonfatal cerebral infarction and retinal infarction in the aspirin-treated group. The authors' conclusions are pertinent to the therapy of TIA's:

> This serves to emphasize the importance of patient selection if platelet antiaggregant therapy is under consideration. Patients in the study who had no lesion or an occlusion of the carotid artery on the side appropriate to their symptoms were not, as a group, benefited by aspirin therapy.[48]

The change in the incidence of transient ischemic attacks after instituting aspirin therapy is additionally important. In 55.8 percent of the patients in the placebo group, there was a reduction in frequency of transient ischemic attacks or no furtner attacks occurred. In the aspirin-treated group there was an 80.8 percent reduction in the frequency of or complete ablation of transient ischemic attacks. The hazard underlying this observation is that transient ischemic symptoms can be masked in a patient in whom there is a progressing stenotic lesion which will nevertheless result in a thrombotic stroke. Therefore, careful surveillance should be maintained in patients who are treated with antiplatelet regimens to make sure that the ulcerated lesion does not progress to one of hemodynamic significance, in which case it should be treated surgically before thrombosis occurs. Indiscriminate treatment of patients with aspirin or other antiplatelet drugs may have undesirable sequelae, inasmuch as the interference with prostaglandin synthesis also blocks the formation of prostacyclin, a potent vasodilating agent with strong antiplatelet actions, produced by vascular endothelial cells. Prostacyclin prevents platelet adhesion and thrombosis on normal arterial endothelium. In a Canadian multicenter study covering 5½ years, aspirin in a dose of 1,300 mg per day was found to protect men in whom transient ischemic attacks had occurred from subsequent stroke or death.[12] The Canadian study analyzed 585 patients who had transient ischemic attacks and were randomly allocated into four treatment groups, each of which took one of the following: placebo, aspirin, aspirin with dipyridamole, or dipyridamole alone. A 31 percent reduction in stroke or death was achieved in the aspirin-treated group when compared with the placebo-treated group. In males, however, there was a 48 percent reduction in the risk of stroke in the aspirin-treated group. Dipyridamole in combination with aspirin, or dipyridamole alone seemed to confer no additional benefit. However, no benefit was found for female patients in the aspirin-treated group or those in the drug-combination groups.

Surgical Therapy

The surgical treatment of stroke dates back to the 1954 report by Eastcott, Pickering and Rob describing a patient with intermittent attacks of hemiplegia who was treated by reconstruction of the internal carotid artery.[62] From that first success, the operation of internal carotid endarterectomy has been widely applied and there are abundant reports in the literature to judge its efficacy and assess its appropriateness.

It has become quite evident that carotid endarterectomy is inappropriate in the treatment for an acute stroke or for the relief of a fixed or evolving neurologic deficit. Disobliteration of an already thrombosed internal carotid artery is likewise usually ineffective. However, when a hemodynamically significant obstructing lesion, or an ulcerating plaque, is encountered which remains symptomatic despite adequate medical therapy, or when a successfully treated ulcerated plaque progresses to the point of hemodynamic obstruction, carotid endarterectomy provides an effective treatment modality. Although relatively simple, safe and effective, this procedure nevertheless demands meticulous operative technique and familiarity with the myriad problems associated with cerebrovascular disease. Analyzing the results of carotid endarterectomy can be a fascinating adventure into the realm of surgical competence. The individual variations often hidden in multicenter trials are easily discerned in the multiple individual and large center results which have been individually published.[63] Morbidity and mortality rates range from none to a high of 25 percent, a rather disconcerting spread, indicating that when surgical correction of these lesions is contemplated, a specialized vascular surgical facility be chosen with care.

The surgical therapy of stroke is prophylactic and therefore depends largely on diagnostic confidence and thorough knowledge of the epidemiology of asymptomatic bruits and transient ischemic attacks. In treating patients with asymptomatic occlusive lesions or transient ischemic attacks, the operation can be carried out with an operative mortality less than 1 percent and morbidity less than 0.5 percent.[16] In a series encompassing over 2,000 patients reported by Rob on a subgroup of 103 patients followed for more than five years, 83 percent remained asymptomatic, one patient died within 30 days of operation, an additional five patients died from strokes and 25 patients died as a result of myocardial infarction during the follow-up period.[64] Incidence of transient neurologic deficit in this group was 3 percent. Thompson, reporting on over 1,000 patients during a 19-year period, indicated an operative mortality of 1.5 percent, which could be subdivided into an operative mortality of 4.2 percent for frank strokes (a condition for which carotid endarterectomy is no longer recommended), a mortality of 0.8 percent for patients with transient ischemic attacks, and no mortality for those with asymptomatic carotid bruits. In 0.7 percent of cases there was some permanent neurologic deficit postoperatively. In the patients with unilateral stenotic lesions and contralateral occlusion, there was no mortality and only a 0.8 percent incidence of neurologic deficit.[16]

In patients with transient ischemic attacks on the ipsilateral side to a complete internal carotid artery occlusion, the presence of stenosis at the external carotid artery orifice must be investigated. The ipsilateral external carotid artery is a major collateral pathway in the presence of internal carotid artery occlusion and contributes significantly to cerebral perfusion. In a patient who has an asymptomatic internal carotid artery occlusion, transient ischemic attacks may begin to develop in that hemisphere when a stenotic plaque develops at the external carotid artery orifice; in a significant number of cases the symptoms will be alleviated by external carotid endarterectomy.

Analysis of the data published on the United States Multicenter Trial of aspirin therapy in cerebral ischemia provides valuable information regarding anticipated benefits from medical and surgical therapy. Relatively homogeneous groups were treated at large medical centers where the emphasis was on competent treatment of cerebrovascular disease.[48,61] In patients assigned to the medical therapy arm of the protocol, a 20-percent incidence of stroke or death occurred within six months of entry into the study, whether the patient was given aspirin or a placebo. Of the 178 participants in that group, 25 had had a thrombotic stroke (14 percent); in 18 of these patients, the stroke occurred on the same side as the original symptoms (10 percent of the entire group). Looked at another way, 72 percent of the patients who had a stroke during the study, regardless of whether they were receiving aspirin or placebo, had the stroke on the side of the symptomatic lesion. In all of these patients, angiographic evaluation had been carried out. Of 130 patients who were assigned to the surgical arm of the protocol, 16 died within two years of follow-up, irrespective of whether the patient was taking aspirin or placebo, a mortality rate of 12.3 percent. Strokes occurred in ten patients (7.6 percent), three of these occurred on the operated side (30 percent). Unfortunately, no strict criteria were developed or adhered to when selecting patients for surgical or medical therapy, inasmuch as the study was designed to assess the effect of

aspirin versus placebo regardless of antecedent therapy. Allocation to surgical therapy and then the treatment protocol was made by the medical and surgical consultants of each medical center. There is, however, a striking difference between the two groups in the overall incidence of stroke (7.6 percent compared with 14 percent). This further underscores the need to assign patients carefully to the proper treatment regimen at the outset, reassessing their progress and modifying the treatment program if the results are unsatisfactory.[65]

A new operative approach has greatly increased the potential number of patients who may benefit from correction of cerebrovascular obstructive disease. These are patients whose cerebral circulation is seriously compromised owing to obstructing lesions that are considered inaccessible to direct surgical correction: (1) patients having transient hemispheric ischemic attacks with occluded ipsilateral internal carotid artery and a normal or enlarged external carotid artery without stenosis, (2) patients having transient ischemic attacks with stenosis of the intracranial internal carotid artery, particularly at the area of the carotid siphon and (3) patients having transient ischemic attacks with stenosis of the middle cerebral artery. The microvascular anastomosis of superficial temporal artery to middle cerebral artery originally reported by Yasargil[66] bypasses the entire internal carotid artery, augmenting the usual external to internal carotid artery collateral channels by direct anastomosis of the normal external carotid artery system, into the intracranial circulation by way of the middle cerebral artery. As experience with this procedure increases, its safety and effectiveness appear to improve and become better established. Of the patients with patent anastomosis, 80 percent have been reported free of symptoms, and the early occlusion rate is about 10 percent.[67] This operation is currently undergoing a multicenter trial.

Summary

Stroke is a prevailing cause of serious morbidity and mortality in the entire Western world. Its cost to patients and society makes it one of the most devastating illnesses suffered by mankind. Although the means of modifying the course of events once the stroke occurs still remain elusive, we have achieved progress in identifying and treating stroke-prone patients. Patients with asymptomatic cervical bruits as well as those having transient ischemic attacks represent a particularly high-risk group for stroke. In a patient with an asymptomatic cervical bruit, noninvasive cerebrovascular testing should be done, and if the tests show a high likelihood of a hemodynamically significant lesion in the internal carotid artery system, angiography should be carried out to define the anatomic position, extent and character of the lesion so that a rational therapeutic protocol can be planned. If there is an ulcerated, nonobstructing lesion in a male patient, therapy should be instituted with aspirin or aspirin combined with persantin. Unfortunately, no satisfactory medical therapy has yet been shown for female patients.

Patients who are managed medically should be carefully watched and reevaluated at six-month to yearly intervals to ascertain whether the bruit has altered in character or whether the noninvasive tests indicate hemodynamic change. It is important to realize that adequate medical therapy can mask symptoms in a lesion that may be progressing to occlusion, and if this occurs surgical intervention should be undertaken. In patients with documented transient ischemic attacks, baseline noninvasive tests should be done so that therapy and progress can be carefully followed up without requiring repetitive angiography. However, initial angiography is highly useful in this group of patients, regardless of the type of therapy employed. The patient's case is then followed at six-month to yearly intervals, depending on the clinically assessed aggressiveness of the general atherosclerotic process. If the noninvasive tests indicate signs of hemodynamic change, operative intervention should be contemplated. If transient ischemic attacks occur, platelet function studies should be repeated, and if platelet function has not altered, the patient should be reinstructed in drug compliance and the dosage increased. If transient ischemic attacks persist despite adequate platelet suppression, operative intervention should be planned, even in cases of nonobstructing ulcerated plaque.[55,68]

If the lesion is stenotic, and if it is greater than 60 percent of the cross-sectional diameter and surgically accessible, it should be treated operatively. If an obstructing lesion is found, successful operative correction of the lesion will provide the best protection against stroke. Patients with a completed stable stroke whose function has significantly improved but who have an extracranial cerebrovascular lesion should be treated as described above, depending on the nature of the

lesion. Although no improvement in the completed stroke is likely, the risk of a new stroke is so high that it jeopardizes the earlier recuperation.[39]

Substantial progress will undoubtedly be made with respect to noninvasive diagnosis and medical therapy, as well as evaluation of newer operative techniques such as the middle cerebral artery to superficial temporal artery bypass. Nevertheless, we now have tools to begin controlling this difficult problem. Our next step must take us beyond investigation and clinical trials to widespread, intelligent application of the diagnostic and therapeutic principles that have been established.

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Specialty Conference

Moderator

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An edited transcription of a Clinical Case Conference arranged by the Department of Medicine of the UCLA School of Medicine (University of California, Los Angeles).

Refer to: Simmons DH, Nash G, Brigham KL, et al: Adult respiratory distress syndrome—Interdepartmental Clinical Case Conference, University of California, Los Angeles (Specialty Conference). West J Med 130:218-235, Mar 1979

Adult Respiratory Distress Syndrome

Many causes for the adult respiratory distress syndrome (ARDS) have been reported, all with common pathologic, pathophysiologic and biochemical end results. The final common pathway may involve changes in lung content of a critical enzyme, superoxide dismutase, or alterations in surfactant metabolism, or both. The early assumption that the disorder is partially due to oxygen toxicity from inspired oxygen concentrations greater than 60 percent is consistent with findings of recent biochemical studies. Although the lung normally maintains its alveoli dry, during ARDS increased permeability of small pulmonary vessels results in primary pulmonary edema, in contrast to edema from increased vascular pressure. These data have been obtained mainly in animals; whether they apply to humans with ARDS is not certain. Tissue oxygenation is improved by increasing end-expiratory pressure in an animal model of ARDS, more effectively during spontaneous breathing than during mechanical ventilation. During spontaneous breathing, adverse ventilatory effects were caused by stimulation of pulmonary reflexes.

DANIEL H. SIMMONS, MD, PHD:* *As there are several excellent reviews of the adult respiratory distress syndrome* (ARDS), *the most recent by Hopewell and Murray,[1] and by Petty and Newman,[2] this symposium will focus on specific areas of current interest in which significant developments are occurring.*

The adult respiratory distress syndrome was first named by Ashbaugh and associates[3] in 1967. In 1971 it was described more completely by

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ABBREVIATIONS USED IN TEXT

ARDS = adult respiratory distress syndrome
CPAP = continuous positive airway pressure
DAD = diffuse alveolar damage
FIO_2 = fractional concentration of inspired oxygen
$Paco_2$ = arterial carbon dioxide partial pressure
Pao_2 = arterial oxygen partial pressure
PEEP = positive end-expiratory pressure
Po_2 = oxygen partial pressure
PS = permeability surface area products
Pvo_2 = mixed venous blood oxygen partial pressure
TLC = total lung capacity

Petty and Ashbaugh[4] when they characterized the syndrome by specific clinical, physiologic, radiologic and pathologic criteria, correlating earlier reports from these fields of interest. Their criteria included the following:

- Clinical—*respiratory distress, tachypnea and cyanosis.*
- Physiologic—*refractory hypoxemia (now known to be caused by increased intrapulmonary shunting) and high inflation pressure during mechanical ventilation (or low lung compliance, the "stiff lung" syndrome).*
- Radiologic—*diffuse alveolar infiltrates.*
- Pathologic *(based on early autopy findings) —pulmonary congestion, hyperemia and formation of hyaline membranes.*

There have been many synonyms for ARDS, *both before and after these descriptions. These include shock lung, traumatic wet lung, adult hyaline membrane disease, acute respiratory failure, postperfusion lung, oxygen toxicity lung, wet lung, Da Nang lung, diffuse alveolar injury, acute diffuse lung injury and noncardiogenic pulmonary edema. Two other names—primary pulmonary edema and diffuse alveolar damage* (DAD)*—will be suggested by participants in this conference. This multitude of synonyms reflects early confusion about the syndrome because the names used were based on various factors: specific causes (such as oxygen toxicity of lung), appearance of the lung (traumatic wet lung), the situation in which the syndrome arose (shock lung), the clinical features (adult hyaline membrane disease), laboratory data (acute respiratory failure) or on pathophysiologic studies (noncardiogenic pulmonary edema). Two of the recent synonyms most commonly used are diffuse alveolar injury and noncardiogenic pulmonary edema, both of which carry implications about the cause and pathophysiology of the disorder.*

TABLE 1.—*Disorders Associated with Adult Respiratory Distress Syndrome**

Shock of any etiology	*Inhaled toxins*
Infectious causes	Oxygen
Gram-negative sepsis	Smoke
Viral pneumonia	Corrosive chemicals (nitrogen dioxide, chlorine, ammonia, phosgene, cadmium)
Pneumocystis carinii	
Cytomegalovirus	*Hematologic disorders*
Trauma	Intravascular coagulation
Fat emboli	Massive blood transfusion
Lung contusion	Postcardiopulmonary bypass
Nonthoracic trauma	*Metabolic disorders*
Head injury	Pancreatitis
Liquid aspiration	Uremia
Gastric juice	Paraquat ingestion
Fresh and salt water	*Miscellaneous*
Hydrocarbon fluids	Lymphangitic carcinomatosis
Drug overdose	Increased intracranial pressure
Heroin	Eclampsia
Methadone	Postcardioversion
Propoxyphene	Radiation pneumonitis
Barbiturates	

*Adapted from Hopewell and Murray.[1]

There has been much controversy about the use of the term adult respiratory distress syndrome, some authors advocating its use because it can act as a unifying concept for directing therapy,[5] others objecting because it may distract from consideration of specific causes, which are often critical in its management.[6]

Although ARDS *is caused by various physical disorders (Table 1), the pathologic and pathophysiologic results are strikingly similar. These consequences include diffuse injury to interalveolar septa, increased permeability of vascular endothelium and alveolar epithelium, intravascular platelet aggregation and many other abnormalities.[7-9] These disorders in turn lead to the classic physiologic, radiologic and pathologic findings. Table 1 is as important in pointing out the many associated disorders as it is in identifying each one. The extent of this list has little effect on whether the term adult respiratory distress syndrome should be used; it does indicate that attention to the cause may be critical.*

Adult respiratory distress syndrome occurs in about 150,000 persons each year, the estimated incidence in 1972.[10] This incidence may still be increasing;[1] however, it is not clear whether the reported increase is due to increased awareness of the disorder or to a true increase in incidence. The mortality due to this disorder is high, probably greater than 50 percent, but there are no exten-

sive data to confirm this. Frequency of diagnosis of milder cases is likely a major factor in determining the mortality. Although the mortality may be decreasing, the decrease is not significant,[1] *despite dramatic improvements in therapy of the disorder. This raises important questions about the true value of the therapeutic modalities developed in recent years and accepted as being valuable.*

Pathology of ARDS

GERALD NASH, MD*

IN THE MIDDLE 1960's when ARDS was emerging as a clinical entity, pathologists were impressed with unusual gross and microscopic appearances of the lungs of patients who had died as a result of the syndrome. In 1967 Drs. Nash, Blennerhassett and Pontoppidan[11] reported on an autopsy study of patients (many with ARDS) who had died in a respiratory intensive care unit. In that study, the lungs of those patients were compared with those of patients in a control autopsy population who had not had acute respiratory failure and who had never been treated with a mechanical ventilator. A wide range of gross and microscopic changes were encountered with approximately equal frequency in the two groups. However, two distinctive lesions were found in the study group that set this group apart from the control population.

The first lesion was characterized grossly by heavy consolidated lungs that had a homogeneous beefy-red appearance. Only a small amount of serosanguineous fluid could be scraped from the cut surface; the foamy pink fluid, characteristic of intraalveolar edema, was not present. Microscopically, such lungs showed capillary congestion, marked interstitial edema, a moderate amount of intraalveolar fibrinous exudate and focal alveolar hemorrhage. The most striking finding, and one which typified this lesion, was the presence of hyaline membranes lining alveolar ducts, alveoli and some respiratory bronchioles.

The second lesion, which separated the study group from the control population, was a pattern of early interstitial fibrosis found in many patients who had died in the respiratory unit. Viewed grossly, the lungs of these patients were characterized by a greyish-pink consolidation without demonstrable exudate, suggesting a degree of fibrous organization. On microscopic examination, there was pronounced interstitial thickening with a combination of edema fluid, histiocytes, fibroblasts, increased reticulin and collagen fibers. The normal alveolar surface had been replaced by large rounded or cuboidal cells, a finding commonly referred to as "hyperplasia of alveolar lining cells" by pathologists. Some lungs in the patients of the study group showed a combination of the two distinctive patterns, with evidence of hyaline membranes undergoing organization and early interstitial fibrosis.

When the pathologic changes were correlated with the duration of ARDS, it became apparent that the two distinctive lesions, which characterized the lungs of the patients in the study group, were really phases in the evolution of a particular type of morphologic response of the lung to injury. In general, patients with ARDS who died after a week or less had the interstitial edema-hyaline membrane pattern. Those who lived two weeks or more had the early interstitial fibrosis pattern, and patients who died after one to two weeks had a combination of the two patterns. The interstitial edema-hyaline membrane lesion was called the exudative phase and the early interstitial fibrosis picture was the proliferative phase of the process.

A closer look at the clinical information available on the study group patients showed that patients with the exudative or proliferative lesions had been treated with toxic concentrations of oxygen for prolonged periods. We concluded that the lesions probably represented phases in the evolution of pulmonary oxygen toxicity in man. Additional studies by other investigators on similar patients with ARDS showed comparable findings and also implicated oxygen toxicity as the likely cause of the lesions.[12-15] Furthermore, the findings in experimental studies showed that the exudative and proliferative lesions described in patients with ARDS could be reproduced in animals by exposing them to toxic concentrations of oxygen for prolonged periods.[16-19]

These studies led to a judicious use of oxygen in the treatment of acute respiratory failure, with an attempt to avoid administering toxic levels unless absolutely necessary to maintain life. In the new enlightened era of oxygen therapy, some patients died with complications of ARDS who had never required and therefore never received toxic concentrations of oxygen. When their lungs were

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examined at autopsy, the same exudative and proliferative lesions characteristic of oxygen toxicity were found. The reason for this is that the morphologic changes seen in ARDS represent a nonspecific reaction of the lung to various deleterious agents.[20] Although these changes are characteristic of pulmonary oxygen toxicity, they are also seen in radiation pneumonitis and influenza pneumonia, and after the inhalation of chlorine, phosgene, carbon dioxide at high tensions and mercury vapor. Ingestion of kerosene and paraquat has been associated with these changes, as have toxic reactions to various drugs including busulfan, bleomycin, cyclophosphamide, melphalan, hexamethonium, nitrofurantoin and methysergide. In addition to specific agents causing this reaction, several conditions are associated with it, including hyaline membrane disease of the newborn, and the group of conditions encompassed by the term ARDS such as shock, trauma, drug coma and sepsis. The name that has been adopted for this reaction is diffuse alveolar damage (DAD).

The development of DAD at the ultrastructural level has been well documented in pulmonary oxygen toxicity, both in experimental animals and in man.[17,21-25] Although DAD not associated with oxygen toxicity in patients with ARDS has not been as thoroughly studied, the evidence that does exist suggests a similar sequence of morphologic alterations.[26,27] The first change that occurs in pulmonary oxygen toxicity is the development of interstitial edema, usually within 48 hours of breathing 100 percent oxygen in most species. At this time there may not be evidence of damage to the alveolar capillary endothelium that could account for a change in capillary permeability; this condition cannot be differentiated from hemodynamic pulmonary edema on a morphologic basis.[21,28,29] However, with continued exposure to toxic concentrations of oxygen (about three to seven days) profound changes occur in the alveolar epithelium and endothelium of alveolar capillaries, with evidence of injury followed by necrosis and eventual sloughing of the cells from their basement membranes. Fibrin-platelet thrombi may develop in the capillaries denuded of endothelium, resulting in exudation of fluid, plasma proteins and some erythrocytes into the interstitial and alveolar spaces. The necrotic alveolar epithelium, mainly type I pneumocytes, plus fibrin and other plasma proteins make up the hyaline membranes characteristic of the exudative phase of DAD. At this stage the lesion clearly differs from hemodynamic pulmonary edema, which is not associated with diffuse necrosis of the cells of the air-blood membrane.[28,29] After necrosis the capillary endothelium and alveolar epithelium regenerate, a process that may be completed in a few days.[17,25,27,30] The cell that is responsible for repopulating the alveolar surface is the type II cell or granular pneumonocyte, the same cell that secretes surfactant.[17,25,27] Granular pneumonocytes vary from large rounded to cuboidal cells. Consequently, when they cover the entire alveolar surface, the alveolar epithelium seems hypertrophied and hyperplastic. While regeneration of epithelium and endothelium takes place, many fibroblasts and collagen fibers become apparent in the interstitium.[17,25,27] These changes constitute the ultrastructural counterpart of the proliferative phase of DAD as seen by light microscopy.

As a common nonspecific reaction of the lung to injury, DAD is not a diagnosis nor does it imply anything about causes. When DAD is found in a patient, it should prompt a careful search of the clinical data for a possible cause. Oxygen toxicity was probably a major cause of ARDS in the days when toxic concentrations of oxygen were administered almost routinely to patients in whom mechanical ventilation was required. Even today, it undoubtedly contributes to the development of DAD in some patients with ARDS. However, there are many patients who die of ARDS in whom the cause of DAD remains unknown.

An important question that confronts pathologists and clinicians today is the natural history of DAD. Diffuse alveolar damage was the lesion seen in the early phase of the Hamman-Rich syndrome, and it probably is an important precursor of idiopathic interstitial fibrosis.[31] Does DAD invariably lead to interstitial fibrosis or can it resolve with little or no residuum? This question has considerable practical significance in ARDS because the technology is available to prolong the lives of patients, either with conventional ventilatory care or with extracorporeal oxygenation. Examination of the lungs of patients dying after prolonged therapy for ARDS has shown that a striking degree of pulmonary fibrosis can develop in a few weeks, rather than months or years as was previously believed.[32,33] Alternatively, some patients with ARDS have prolonged clinical courses and recover completely. Presumably, these persons had significant pulmonary changes that resolved. It is generally believed that the exudative phase of DAD is potentially reversible and a well-devel-

oped proliferative lesion is not compatible with resolution.[32] However, a recent study by Koeniger[34] has cast doubt on this concept. In this study lung biopsy studies were done on patients with ARDS who eventually survived with little or no functional impairment. Findings in these studies were similar to those in biopsy studies from patients who did not survive, with some biopsy specimens from each group showing a well-developed proliferative phase of DAD. This study has shown that survival is possible with extensive lung damage and that the finding of the proliferative phase of DAD in a lung biopsy study does not necessarily mean that the prognosis is hopeless. However, a disturbing conclusion of this work is that, at present, morphologic criteria do not exist that would enable a pathologist to predict the outcome of ARDS from a biopsy study showing DAD. It is hoped that this situation will change as more data from studies involving sequential lung biopsy studies become available.

Lung Vascular Permeability and Primary Pulmonary Edema

KENNETH L. BRIGHAM, MD

STUDIES BY Guyton and Lindsey[35] suggest that the lung is normally dry because the plasma oncotic pressure (absorption force) exceeds the microvascular hydrostatic pressure (filtration force).[35] Alveoli are normally dry, but the lung as a whole contains much water.[36] The mechanisms for keeping alveoli dry are more complicated than originally believed.[36-38]

What Keeps Alveoli Dry?

Lung Lymph Flow

Under normal conditions lymph flows from the lung; this indicates that the net Starling forces are normally favoring filtration in the lung as in all other organs. When hydrostatic pressure is increased in exchanging vessels, lymph flow increases even at pressures too low to cause edema (Figure 1).[36,39,40] Therefore, when filtration is increased, lymph flow increases (about double for a 15 cm of water microvascular pressure increase) and this prevents fluid from accumulating in the lung.

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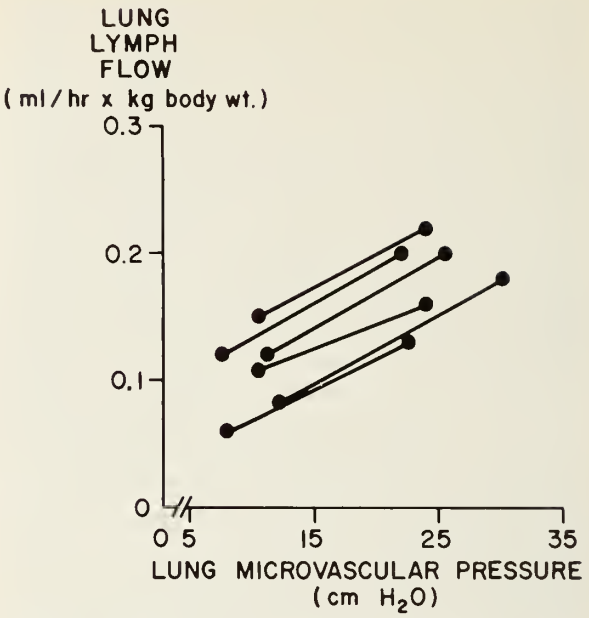

Figure 1.—Effects of mechanically increased lung vascular pressure (left atrial balloon inflation) on lung lymph flow in awake sheep. Microvascular pressure is left atrial pressure plus 0.4 (pulmonary artery pressure minus left atrial pressure). Moderate pressure increases cause lymph flow to increase. Lymph flow doubles for a 15 cm of water microvascular pressure increase.

Interstitial Oncotic Pressure

All of the small molecules in plasma equilibrate with the interstitial space so that the main solutes exerting osmotic forces across exchanging vessel walls are proteins. In the lung, effective interstitial (lymph) protein concentration is normally high (about two thirds of the plasma concentration).[36-41] If interstitial protein concentration could fall relative to plasma, this would increase the osmotic force favoring absorption and thereby help protect against excessive filtration and edema. Figure 2 shows what happens when hydrostatic pressure is increased in lung vessels: lymph flow goes up and lymph protein concentration goes down.[36]

There is nothing miraculous about the fall in filtrate protein with increasing filtration rate; that is exactly how a semipermeable membrane ought to behave.[42] Because water moves freely across the membrane and proteins are restricted, increased pressure causes a relatively larger increase in water flux. As lymphatics drain the filtrate away from the interstitial space, a "wash-down" of interstitial protein concentration occurs.[36,42] Consequently, the decrease in interstitial oncotic pressure is a negative feedback that normally off-

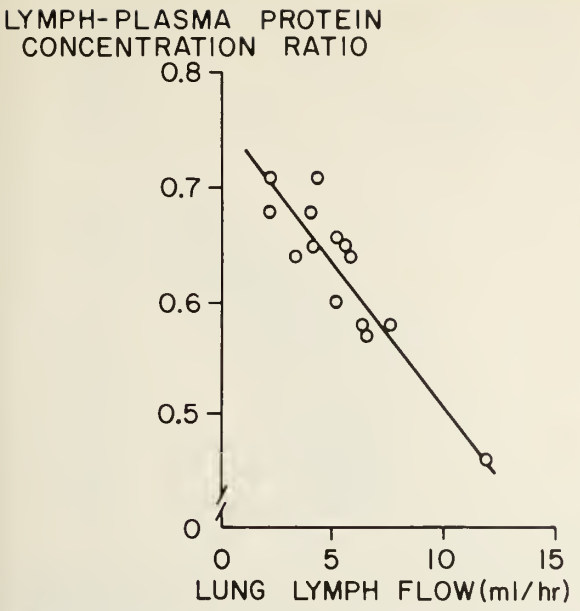

Figure 2.—Steady state lymph/plasma total protein concentration as a function of lymph flow during mechanically increased vascular pressure. Lymph/plasma protein falls as a linear function of increasing lymph flow.

sets about half the microvascular pressure increase.[36,37]

Interstitial Hydrostatic Pressure

If hydrostatic fluid pressure around exchanging vessels increases as fluid accumulates, this, like falling interstitial oncotic pressure, would decrease filtration. Whether this happens in the lung is not known.[37]

The Interstitial Fluid Reservoir

The climax of the pulmonary edema story is alveolar flooding. There is not much interference with gas exchange until alveoli flood, and this occurs only at the end of the story. The lung can store much fluid in the peribronchial and perivascular spaces before alveoli flood.[43] Figure 3 shows a lung with interstitial edema. The alveoli are full of air, but there are large cuffs of fluid (actually ice as the lung is frozen) around vessels and airways.

The potential spaces around airways and vessels form a reservoir that permits filtration from microvessels to exceed lymph flow for some time before alveoli flood. This occurs because alveolar epithelium is tight—highly impermeable—and consequently the resistance to fluid and solute entry into the enormous alveolar space is very high.[44] Why fluid and protein eventually enter alveoli is another story.[45]

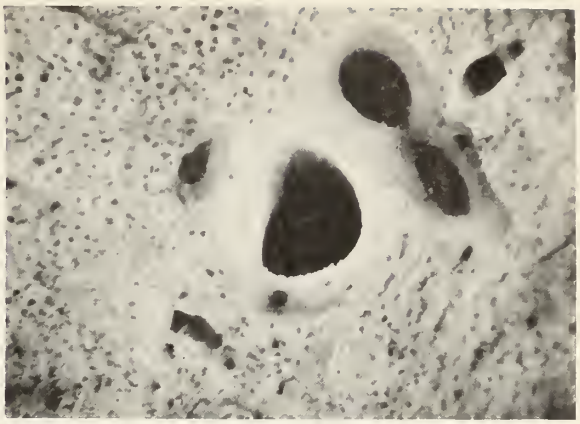

Figure 3.—Photomicrograph of a quick frozen lung in the early stages of edema. Cuffs of fluid (ice) are present around the vessels and airways (the interstitial "reservoir") but there is no fluid in alveoli (Courtesy of Dr. Norman Staub).

What Happens If Lung Vessels Are Too Leaky?

When the left side of the heart fails, pulmonary vascular pressures rise and "high pressure" lung edema may occur; that is, secondary pulmonary edema—secondary to heart failure. Primary pulmonary edema is edema resulting primarily from changes in the lung circulation. Primary pulmonary edema is diagnosed by the presence of edema that cannot be explained by increased left atrial pressure. In this situation, the usual inference is that exchanging vessels are leakier than normal. Lung microvessels are too leaky in the disorders lumped together as ARDS. Although there may be other problems, primary pulmonary edema is apparently a major part of it.

Lung Lymph Flow

When lung exchanging vessels are too leaky (increased permeability), lymph flow (net filtration) is higher than normal for a given microvascular pressure.[38,40,41,46] Figure 4 shows data taken during increased vascular permeability induced by Pseudomonas bacteremia in sheep. Although pressure was increased slightly after Pseudomonas bacteremia, lymph flow was several fold higher than with mechanically increased vascular pressure. What that means is exactly what would be expected. When microvessels are too leaky, the relation between microvascular pressure and filtration (lymph flow) is very steep.

This steep relation between filtration and pressure is both bad and good. The bad aspect is that even small elevations in pressure may profoundly

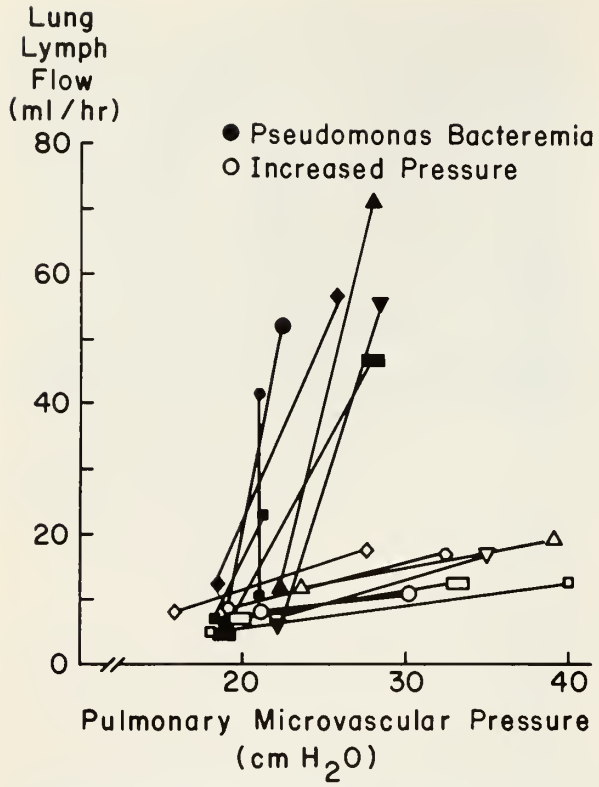

Figure 4.—Comparison of effects of mechanically increased pressure and increased vascular permeability caused by Pseudomonas bacteremia on steady state lung lymph flow in sheep. A different shaped symbol is used for each animal. Lymph flow was much higher during increased permeability even though pressure was low (from Brigham, Woolverton, Blake et al;[38] reproduced by permission of Journal of Clinical Investigation).

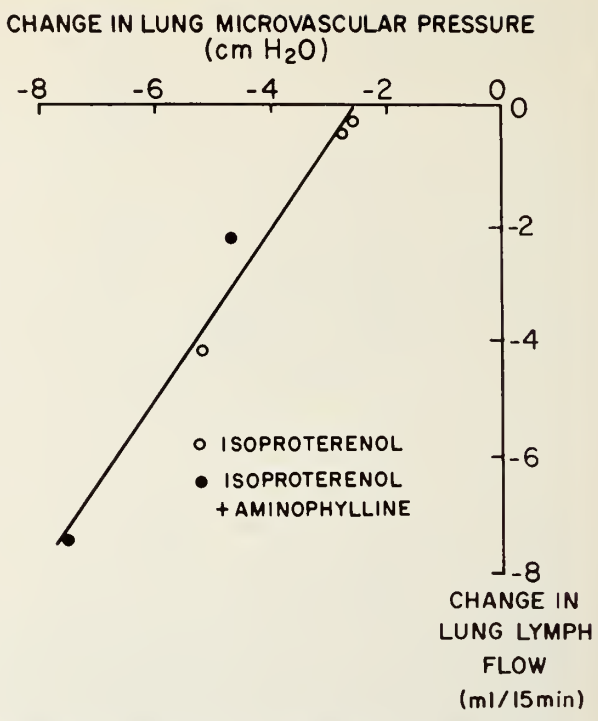

Figure 5.—Effects of isoproterenol and aminophylline infusion on lung vascular pressure and lymph flow, during increased permeability caused by Pseudomonas bacteremia in sheep. The drugs caused both pressure and lymph flow to fall. The relationship between pressure and lymph flow is steep (from Foy, Marion and Brigham,[47] reproduced by permission of Journal of Applied Physiology).

increase filtration when permeability is increased. The good aspect is that even small reductions in pressure may profoundly decrease filtration when permeability is increased.[47] During the steady state of increased permeability response to Pseudomonas in sheep, we infused isoproterenol and aminophylline and measured effects on lung vascular pressures and lymph flow (Figure 5). There were pronounced decreases in lymph flow (net filtration) with even small decreases in microvascular pressure.[48] When lung vascular permeability is increased, it is important to keep pulmonary vascular pressures as low as possible.

Interstitial Oncotic Pressure

Interstitial oncotic pressure falls when microvascular filtration is increased because of increased pressure due to microvessel walls sieving proteins—that is, the proteins have trouble getting across. When the vessels are more leaky, proteins have less trouble getting across (less sieving); therefore, interstitial protein concentration (and thus oncotic pressure) cannot fall as much with increasing filtration rate as it normally would.[38,40,41,46,49] Normally, the lymph/plasma protein concentration falls as a linear function of increasing lymph flow (Figure 6). This occurs whether pressure is increased mechanically or pharmacologically (serotonin).[39,49] But when permeability is increased (in Figure 6 by histamine infusion), there is only a slight fall in lymph protein concentration even at very high filtration rates. The negative feedback effect of falling interstitial oncotic pressure is diminished or lost, depending on how leaky the sieve becomes (that is, how much permeability is increased).

In our experiments with sheep, sieving of proteins is never completely lost. The largest permeability increases occur after Pseudomonas bacteremia and even then there is still sieving of proteins by the blood lymph barrier based on molecular size of the proteins (Figure 7).[41]

When exchanging vessels in the lung are too

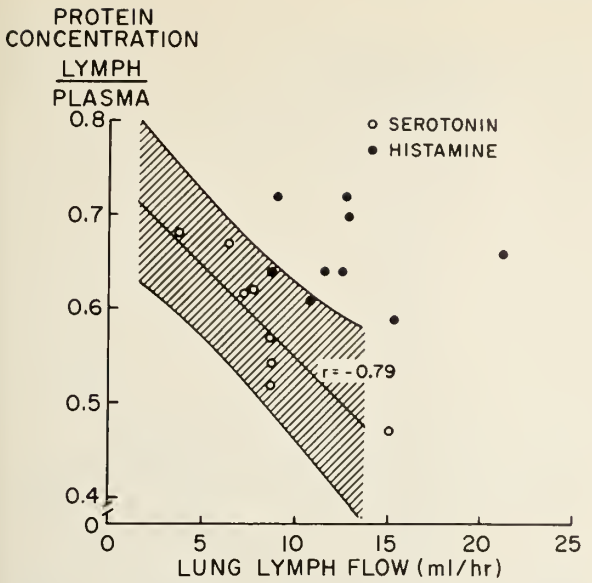

Figure 6.—Relationship between lymph/plasma total protein concentration and lymph flow in sheep. The line and shaded area are the regression line and 95 percent confidence limits for increased pressure studies. The effects of serotonin infusion are indistinguishable from pressure data, but histamine infusion increases vascular permeability so that lymph protein stays high even at high lymph flows (from Brigham and Staub;[49] reproduced by permission of National Heart and Lung Institute).

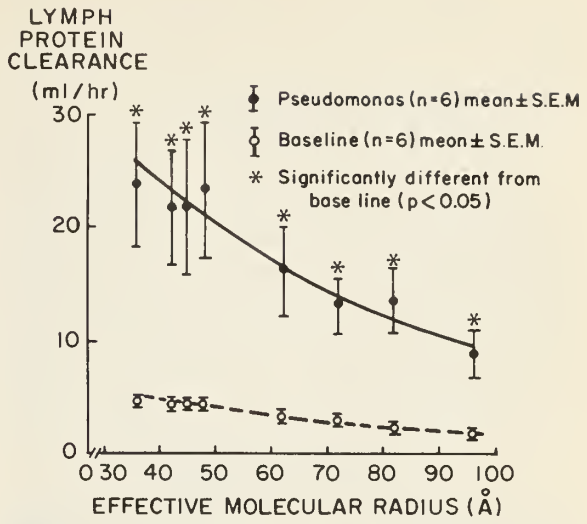

Figure 7.—Steady-state lymph clearance (flow × lymph/plasma concentration) for eight endogenous proteins as a function of molecular radius in sheep. During increased permeability after Pseudmonas infusion clearance of all eight proteins is dramatically increased, but sieving persists reflected in decreasing clearance with increasing molecular size (from Brigham, Owen and Bowers;[41] reproduced by permission of Microvascular Research).

leaky, not only does more fluid get filtered for a given pressure, but the interstitial proteins do not "wash down" as much. Consequently, the effects of increased or decreased microvascular pressure are even more exaggerated.

Interstitial Hydrostatic Pressure

My guess is that if interstitial fluid pressure around exchanging vessels increases during fluid accumulation, then it should occur with both increased permeability and high pressure edema. That may be a poor guess because the compliance of the interstitium or the volume of the microvascular bed or even alveolar epithelial permeability may change in conditions where vascular permeability is increased. Any of these factors could at least theoretically affect interstitial fluid pressure.

The Interstitial Fluid Reservoir

In dogs with alloxan pulmonary edema (increased permeability edema) the sequence of fluid accumulation is similar to that in high pressure edema.[43] Fluid accumulates first in the spaces around vessels and airways and only after that are alveoli flooded. In that condition the interstitial reservoir protects alveoli. But suppose alveolar epithelial permeability was increased dramatically. Since the main filtration site is in alveolar vessels,[37] this could make a direct path for microvascular filtrate to alveoli, bypassing the interstitial reservoir altogether. I do not know if this ever happens, but if so it would be devastating, especially if capillaries are also very leaky.

Summary of Lung Edema Protective Mechanisms

The main variables that normally keep alveoli full of air instead of fluid are summarized in Table 2. Normally, in response to increased vascular pressure, lymph flow goes up, interstitial oncotic pressure falls, interstitial fluid hydrostatic pressure may rise, filtration (lymph flow/microvascular pressure) falls (because of falling interstitial oncotic pressure) and fluid accumulates first in the perivascular and peribronchial reservoir. When exchanging vessels are leakier than normal, lymph flow increases considerably, interstitial oncotic pressure falls less for a given lymph flow (or not at all, or rises, depending on how extensive the leak is), what happens to interstitial fluid pressure is unknown, lymph flow/microvascular pressure increases tremendously and the interstitial reservoir still fills first (unless,

of course, there are some situations where it does not).

Can Lung Vascular Permeability Be Measured In Humans?

Because there have been no methods for measuring permeability in humans, no one knows, except by inference, what role increased lung vascular permeability plays in the pathogenesis of ARDS. In dogs and sheep we have shown that lung vascular ^{14}C-urea permeability surface area products (PS) (calculated from single transit indicator dilution curves) are reproducible and track lung lymph data in various experimental conditions.[50-53] When lymph data show increased permeability, urea PS goes up; when lymph data do not show increased permeability, neither does urea PS. We are now making the indicator PS measurements in humans.

TABLE 2.—*Summary of Lung Edema Protective Mechanisms*

Protective Mechanism	*Increased Pressure*	*Increased Permeability*
Lymph flow	↑	↑↑
Perimicrovascular oncotic pressure (IIpmv)	↓↓	→↑↓
Perimicrovascular hydrostatic pressure (Ppmv)	?↑	?↑
Lymph flow / Microvascular pressure	↓	↑↑
Interstitial reservoir	↑	↑?

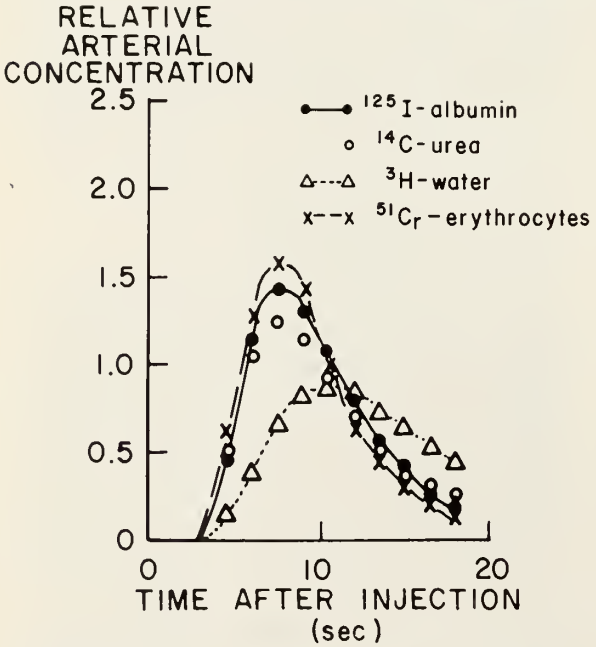

Figure 8.—Transpulmonary time—concentration curve for four indicators in a human. ^{14}C-urea permeability surface area product (PS) can be calculated from the difference between the urea and intravascular (^{51}Cr-erythrocyte and ^{125}I-albumin) curves (from Brigham, Snell, Marshall, et al,[54] reproduced by permission from American Heart Association, Circulation Research).

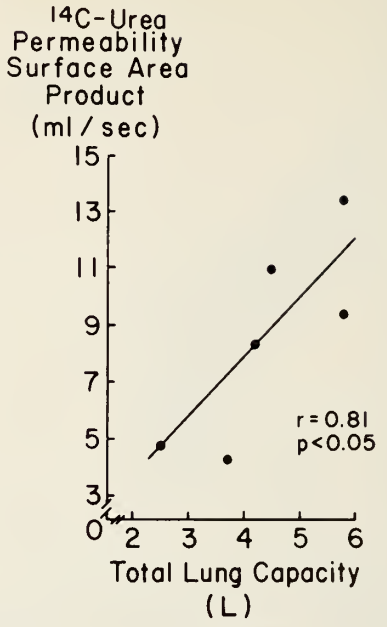

Figure 9.—Lung vascular ^{14}C-urea PS as a function of total lung capacity (TLC) in six humans. The correlation is good.

Figure 8[54] shows the transpulmonary time concentration curves for the four indicators used in a human. Both ^{51}Cr-erythrocytes and ^{125}I-albumin are intravascular indicators; ^{3}H-water tags the accessible water space and the distribution of ^{14}C-urea is limited by the microvascular endothelial barrier. The PS is calculated from the difference between the urea and intravascular curves.[50]

Figure 9 shows lung urea PS as a function of total lung capacity (TLC) measured by the usual helium dilution methods in six patients in whom cardiac catheterization was done. If the PS is accurate, it ought to correlate with lung size, that is, surface area. If TLC is a reasonable estimate of lung size, the correlation is good. We have shown repeatedly in animals that lung vascular urea PS does not increase with increased vascular pressure and this also seems to be true in humans (Figure 10).[55]

Findings in these studies encourage us to believe that urea PS may be a good way to measure lung vascular permeability in humans. This may

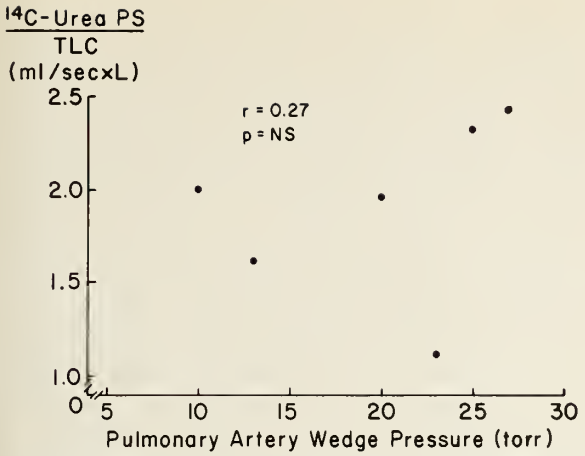

Figure 10.—^{14}C-urea PS normalized to TLC versus pulmonary artery wedge pressure in six humans. PS does not correlate with pressure.

make it possible to clarify the role of vascular permeability changes in the various disorders we call adult respiratory distress syndrome.

Oxygen Toxicity*

DONALD F. TIERNEY, MD†

WHAT IS A "safe" concentration of oxygen to give patients? That is one of the most common questions asked by physicians when managing patients with the respiratory distress syndrome. If we ignore the effect of oxygen on the control of breathing and then make a schematic plot of abnormal cell function or mortality against oxygen partial pressures (P_{O_2}), we would observe a curve that is roughly "U" shaped. The increasing mortality at low P_{O_2} reflects increasing hypoxia and, although it is not a true toxic effect, it has the same result, that is, abnormal function or death. The increasing mortality with increasing P_{O_2} is considered a toxic effect and the mechanisms of this toxicity are beginning to be understood. Obviously, the "safe" concentration of oxygen is somewhere on the flat part of the curve, and we need to know where that flat portion ends and the curve rises again. When the P_{O_2} corresponds to inhaled oxygen concentrations of 12 percent to 50 percent, there is little evidence that the exposed lung is significantly different from the lung exposed to air. However, the length of time for these studies is short when compared with a lifetime in man. Therefore the effects of 50 percent oxygen may be significant during a period of weeks, particularly if the lungs are abnormal. Recent reports of prolonged life of residents who live at high altitude (where the P_{O_2} is low) have led some investigators to suggest that the P_{O_2} in air at 1 atm may be toxic during a period of years. There are, however, other theories that may explain the unusually long lives of some people at high altitudes. Nevertheless, the lowest point of a hypothetical curve (plotting oxygen toxicity against the P_{O_2}) may not correspond to the P_{O_2} in air at 1 atm. This intriguing possibility may depend on the relative activities of various metabolic defense mechanisms involved in destroying toxic by-products of oxygen metabolism.

The physician treating patients with severe hypoxemia is caught in a bind because the P_{O_2} in the lung, which may be necessary to provide adequate arterial blood P_{O_2} (P_{aO_2}), may be toxic to the lung. Therefore, patients with a respiratory distress syndrome may have harmful effects from oxygen at both ends of the "U" shaped curve described above. When 100 percent oxygen is given to a patient with a respiratory distress syndrome, the ventilated portions of the lung may become toxic because of hyperoxia; this occurs even though the P_{aO_2} may be so low that the patient could die of hypoxia in other organs.

A "safe level" of inspired oxygen therefore depends on the lowest P_{aO_2} the physician considers to be safe for his patient and the fractional concentration of inspired oxygen (F_{IO_2}) necessary to provide that P_{aO_2}. If this F_{IO_2} is above 50 percent to 60 percent, the physician will need to consider other methods to raise the P_{aO_2} or balance the risk of a low P_{aO_2} against the possible effects on the lung of oxygen toxicity. A young and healthy patient may be able to tolerate P_{aO_2} in the range of 40 to 50 torr, whereas an elderly patient with cardiovascular disease may require a P_{aO_2} above 60 to 70 torr. However, mild toxic effects can be detected with an F_{IO_2} between 40 to 60 percent. As the F_{IO_2} approaches 80 percent, severe, but not lethal, toxic effects appear in previously normal animal lungs; an F_{IO_2} above 90 percent is frequently lethal within three to four days. All of these statements are based upon observations made on normal lungs and the physician must consider factors that may change the toxicity. For example, the mortality of young rats exposed to 100 percent oxygen is much less than that for

*Throughout this discussion the ambient pressure is assumed to be 1.0 atm; therefore, 50 percent oxygen would correspond to a P_{O_2} of 0.5 atm.

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older rats.[56] Furthermore, body weight is an important variable: heavy rats die sooner in oxygen than smaller rats of the same age.[56] Although such individual variation to oxygen toxicity can be determined with animals, similar studies cannot be done with humans. If we understand the basic mechanism of oxygen toxicity from animal studies, we may be able to estimate the likelihood that differences in sensitivity to oxygen toxicity exist among humans.

In predicting the degree of sensitivity to oxygen toxicity perhaps the most important variable may be concurrent lung disease. Dr. Nash has described the pathologic conditions of the respiratory distress syndromes and of oxygen toxicity, both of which produce similar abnormal changes in the alveolus. These include hyaline membranes, injury to the epithelial cells and capillary injury. Therefore, if a patient has a respiratory distress syndrome, one must question whether oxygen, which can cause additional injury to the same cells, may become more toxic at lower partial pressures, that is, injured cells may be more sensitive to oxygen toxicity than normal cells. Perhaps the high F_{IO_2} may produce a transient increase of Pa_{O_2}, but during a period of several days the oxygen toxicity may cause progressive lung injury followed by progressive hypoxemia.

Lungs with the respiratory distress syndromes may be unusually sensitive to high concentrations of oxygen. Fisher and associates[57] noted that rats with a respiratory distress syndrome produced by paraquat (1, 1′ dimethyl-4, 4′-bipyridylium dichloride) die sooner if they are placed in 100 percent oxygen at 1.0 atm. We[58] also found a similar effect in mice with influenza pneumonia, who die sooner if they are placed in 100 percent oxygen than control mice with no pneumonia but exposed to 100 percent oxygen.

In addition to the abnormal changes in alveoli of humans and animals, an indirect effect of oxygen leading to increased sensitivity to infection may also be important clinically. Oxygen at high partial pressures adversely affects several major defense mechanisms against infection. Removal of inhaled bacteria and secreted mucus from airways is mainly dependent on ciliary function.[59] There is evidence that the cilia are rapidly affected by oxygen[60] and the transport of inhaled particles, such as bacteria, out of the airways may be greatly decreased. If bacteria, secretions and inflammatory products are not cleared rapidly from the lung, a greater opportunity for infection would be present. Furthermore, the major defense mechanism against infection in the alveoli is dependent on the function of alveolar macrophages.[59] High concentrations of oxygen for several days have been shown to cause morphologic as well as functional changes in alveolar macrophages, which would probably decrease their ability to kill bacteria.

Although there has been evidence for many years that humans develop oxygen toxicity, it has not been fully accepted until recently.[25] Nearly all studies of the mechanisms of oxygen toxicity have, of necessity, used animals. Potentially, there are several defense mechanisms that may protect against oxygen toxicity and other forms of lung injury.[56] These mechanisms may be responsible for the phenomenon of tolerance, or adaptation, occurring in many animals and probably in humans.[56,61] Large rats die within three days if they are placed in 100 percent oxygen at 1.0 atm. Nevertheless, if rats of the same age and size are placed in 85 percent oxygen at 1 atm for 5 to 7 days, they can subsequently tolerate exposure to 100 percent oxygen for 30 days or longer. Augmented defense mechanisms are probably responsible for the change of sensitivity. It seems likely that the same phenomenon occurs in humans and it may explain the occasional case reports of persons exposed to very high concentrations of oxygen for prolonged periods of time with eventual survival. These reports have been considered to indicate that oxygen toxicity does not occur in humans; the reports, however, are consistent with the patient developing decreased sensitivity as occurs in animals.

Defense mechanisms in the alveolus may include the cellular changes of the epithelium described by Dr. Nash, such as a proliferation of type II cells and perhaps displacement of other type I cells by younger ones. Type II cells, and possibly younger type I cells, have less sensitivity to injury than the original epithelium. However, the main question is why do these and other cells seem to be less sensitive to oxygen toxicity. There are several possible explanations based mostly on metabolic mechanisms.

One mechanism that protects cells from toxic by-products of oxygen metabolism has been studied by Fridovich,[62] who found that oxygen metabolism may involve a single electron reduction of molecular oxygen, producing superoxide anion. This anion, or some of its by-products, may be extremely toxic. Furthermore, all cells (as well

as bacteria) that metabolize oxygen, contain the enzyme superoxide dismutase, which rapidly converts superoxide anion to less toxic products. Some enzyme systems producing superoxide anion are dependent on the partial pressure of oxygen and, therefore, this mechanism could be toxic at higher Po_2. Animals that became less sensitive to oxygen toxicity by previous exposure to 85 percent oxygen at 1.0 atm have increased activity of superoxide dismutase.[63] Superoxide anion may not only be involved in many inflammatory processes but it may also be important in protecting tissues against injury.

Another possible defense mechanism against oxidants exists in the erythrocyte and is dependent upon the presence of the hexose monophosphate-shunt and the reduction of glutathione. Hexose monophosphate-shunt may be important in the lung by providing nicotinamide adenine dinucleotide phosphate (NADPH), which may be used either to reduce glutathione and protect from other oxidants or to resynthesize injured cellular components.[56,64,65]

Recently, Dr. Abe and I[66] have been studying lipid metabolism in lungs of rats recovering from three days of exposure to 100 percent oxygen. Immediately after exposure to oxygen there is a relatively small increase in saturated phosphatidylcholine. However, after recovering in air for two to four days, the saturated phosphatidylcholine almost doubles in content and there are also pronounced increases in the incorporation of precursors, such as palmitate, glycerol and lysophosphatidylcholine, into the saturated phosphatidylcholine of lung slices. Furthermore, if the animals are given large doses of hydrocortisone, approximately 15 mg per kg of body weight every 12 hours, the saturated phosphatidylcholine is about 30 percent more than in lungs of rats exposed to oxygen but given 0.9 percent sodium chloride solution instead of hydrocortisone.

The type II epithelial cells, which increase after oxygen toxicity, contain large quantities of saturated phosphatidylcholine as a component of the pulmonary surfactant. Therefore, our findings are consistent with the evidence that the type II epithelial cells proliferate after injury from oxygen and that this proliferation may be increased by giving hydrocortisone. We also confirmed findings in earlier studies by Sahebjami, Gacad and Massaro[67] who found that hydrocortisone leads to a more rapid decrease of lung weight after oxygen toxicity than if the animals were given a control injection of 0.9 percent sodium chloride solution. Furthermore, the content of DNA did not increase significantly in lungs of animals receiving hydrocortisone, whereas it did increase in the control animals. The interpretation of the DNA data is perhaps related to a decrease of the content of inflammatory cells of the lung when hydrocortisone is given, but one might also expect more DNA as the type II cells proliferate.

Therapy of ARDS: Positive End-Expiratory Pressure

DANIEL H. SIMMONS, MD, PhD

I SHOULD LIKE to present some therapeutic measures that have received some degree of acceptance for ARDS. As I shall discuss in detail the usefulness of a relatively new modality of therapy, maintenance of increased lung volumes by continuous positive end-expiratory pressure (PEEP), I will mention other modalities only briefly.

Since life-threatening hypoxemia is the most outstanding manifestation of ARDS, high inspired concentrations of oxygen should be beneficial. Although this is often helpful in mild cases, it may not adequately oxygenate arterial blood in severe ones and, as previously reported by Drs. Nash and Tierney, may in itself lead to worsening of the condition.

Fluid management is critical in therapy of ARDS. Fluid administration to increase blood volume is occasionally necessary to avoid hypoperfusion caused by decreased cardiac output, especially during PEEP. However, treatment of ARDS usually requires the contrary procedure—fluid restriction or diuresis, or both—to decrease small vessel pressure and lung water content and to reverse the basic abnormality, as discussed by Dr. Brigham. The value of infusing colloid-containing solutions to decrease the pulmonary edema or to treat hypoperfusion is questionable; it probably leads to an increase in lung water and worsening of the condition as much as does administration of crystalloid solutions.

Heparin was originally used because platelet thrombi were found in the lungs of many patients. However, this modality remains controversial; there is little substantial evidence that it reduces morbidity or mortality.

The use of steroids to prevent inflammatory changes in the alveolar wall is also controversial.

There is no substantial evidence that these drugs reduce morbidity or mortality, despite indirect evidence from animal experiments—as discussed previously by Dr. Tierney—that they might be beneficial.

Extracorporeal membrane oxygenation (ECMO) has been tried as a temporary means of maintaining tissue oxygenation. It might be used when lung gas exchange for oxygen has deteriorated to the point where it can no longer maintain life or when dangerously high concentrations of oxygen must be administered for prolonged periods. Extracorporeal membrane oxygenation is at present in the experimental stage.

Maintaining alveoli and airways patent by continuously or periodically increasing lung volume has been accepted as a major advance in the therapy of ARDS; it has been shown to improve both inadequate arterial oxygenation and low lung compliance, two of the major physiologic defects. However, the critical question of whether these maneuvers improve oxygenation of tissues has not been established, because concomitant worsening of tissue perfusion may negate the potential benefit of improving arterial oxygenation.

Therapy aimed at improving patency of alveoli and airways has included use of large tidal volumes (when the patient is on a mechanical ventilator), periodic hyperinflation (during either spontaneous breathing or mechanical ventilation), and the usual methods for clearing of airway secretions.

The most extensive advance in the treatment of ARDS is maintenance of continuously increased lung volumes by PEEP. Despite dramatic improvements in arterial oxygenation[68-73] and related lung compliance,[70,73] we do not have definite evidence that PEEP is of value in all patients or even that it is not detrimental in many others.

Positive end-expiratory pressure has been used most often with mechanical ventilation, as first suggested by Petty and Ashbaugh in 1971.[4] Continuous positive airway pressure (CPAP) during spontaneous breathing, first recommended by Gregory and associates[74] for use in the infant respiratory distress syndrome, has also been used recently in the adult syndrome.[71-73,75] And even more recently, the combination of PEEP and CPAP, with intermittent mandatory ventilation (IMV) and a combination of spontaneous breathing and mechanical ventilation, has been suggested to avoid different adverse effects of both PEEP and CPAP.[76]

In many but not all studies, a major complication of PEEP has been a decrease in cardiac output and oxygen delivery with potentially worsened tissue oxygenation, despite its beneficial effect on arterial oxygenation.[1,68,72] This complication might be avoided by use of CPAP during spontaneous breathing,[71,72,75] although hemodynamic effects of CPAP have not been systematically studied in ARDS.[77] On the other hand, CPAP results in adverse and potentially serious ventilatory responses.[76,78,79] However, this has not been well documented; the thorough review of CPAP by Downes[72] does not even include this potential complication.

Therefore, Dr. Gothe and I did a systematic study of hemodynamic and respiratory responses of a model of ARDS induced by intravenous infusion of oleic acid into anesthetized dogs.[73,80] Eight of these dogs were subjected to various end-expiratory pressures during mechanical ventilation (PEEP) and six to the same levels of end-expiratory pressure during spontaneous breathing (CPAP).

There were several objectives: The first was to determine and compare both hemodynamic and ventilatory responses with the two types of increased end-expiratory pressure. The second was to determine whether there was improved tissue oxygenation with either technique, as shown by changes in the oxygen tension of mixed venous blood (P_{VO_2}), an indicator of the state of tissue oxygenation.[81] The third objective was to determine whether pulmonary reflexes, arising in the lung, played a role in the ventilatory responses to CPAP and if they had an adverse effect on ventilation.

This study was designed to avoid the following problems associated with most reports about the use of PEEP and CPAP: (1) In many studies, P_{aO_2} was adequate, if not normal, before administration of PEEP, which would therefore not be clinically necessary. Under these conditions, the only possible important effect is a decrease in cardiac output and oxygen delivery because of only minor potential for improvement in arterial oxygen content. (2) In most studies, the state of tissue oxygenation was not assessed by criteria such as P_{VO_2}. Although oxygen delivery was often reported, it has not been an adequate criterion for estimating the state of tissue oxygenation; it does not correlate well either with changes in tissue P_{O_2} or development of lactic acidosis. (3) Several studies were done on patients without ARDS but with other diseases, such as chronic obstructive pulmonary disease (COPD) or congestive heart failure.

(4) Many studies were conducted with levels of PEEP inadequate to produce significant changes in severe ARDS. (5) Although findings in some studies showed effects on Pvo_2, the changes were of questionable statistical significance.

In this study, while the dogs breathed 100 percent oxygen, sufficient oleic acid and intravenous fluids were given so that Pao_2 was less than 60 mm of mercury, a condition in which some type of PEEP is thought to be necessary. Measurements were made without any end-expiratory pressure (0 PEEP) and at end-expiratory pressures of 5, 10, 15, 20 cm of water. The means and standard errors of Pao_2 at the various end-expiratory pressures (Figure 11A) confirm that increasing levels of end-expiratory pressure progressively improve arterial oxygenation. The effects of PEEP and CPAP, although statistically different at some levels, would not be significantly different therapeutically.

Figure 11B shows that improvement in arterial oxygenation is due principally to a decrease in

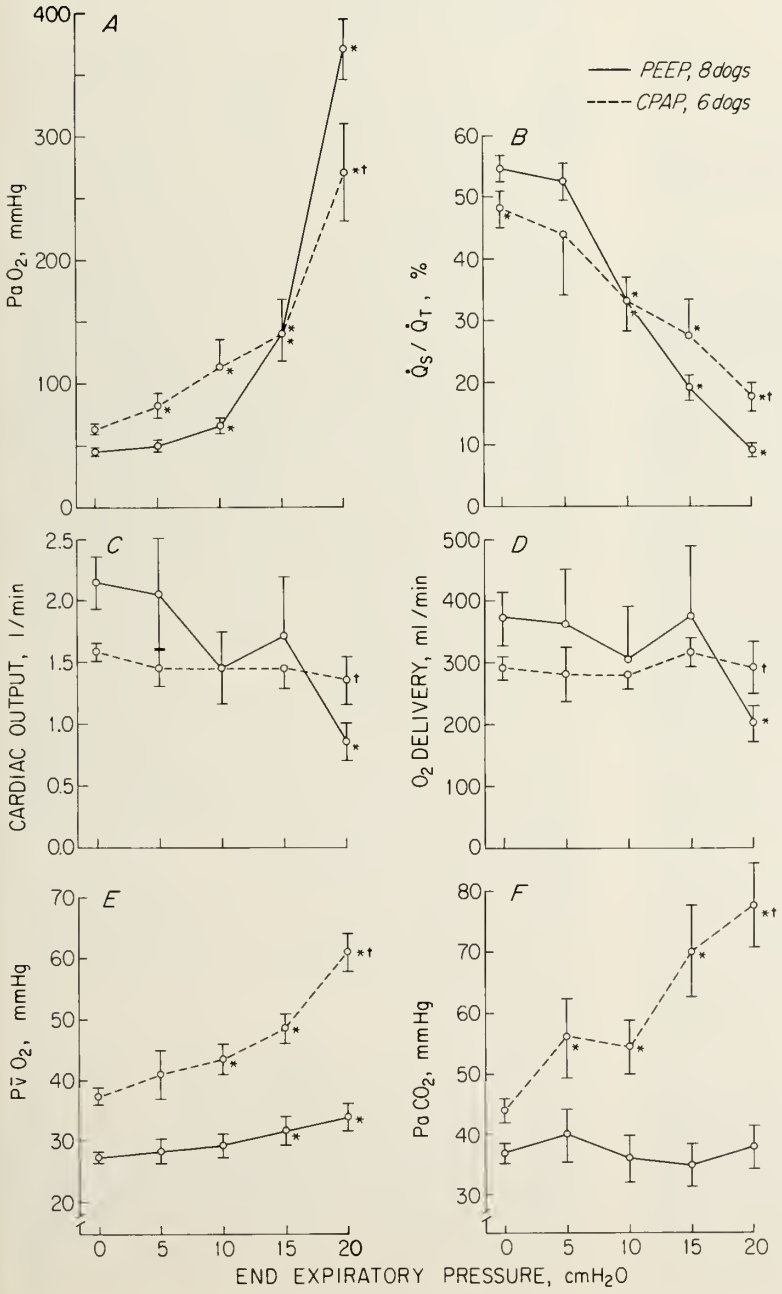

Figure 11.—Mean and standard error at 0, 5, 10, 15 and 20 cm of water of positive end-expiratory pressure (PEEP) during mechanical ventilation **(solid lines)** and the same levels of continuous positive airway pressure (CPAP) during spontaneous breathing **(dashed lines).**

* = significant differences from values at 0 cm of water.
† = significant differences between means for PEEP and CPAP at 20 cm of water. See text for detailed discussion.

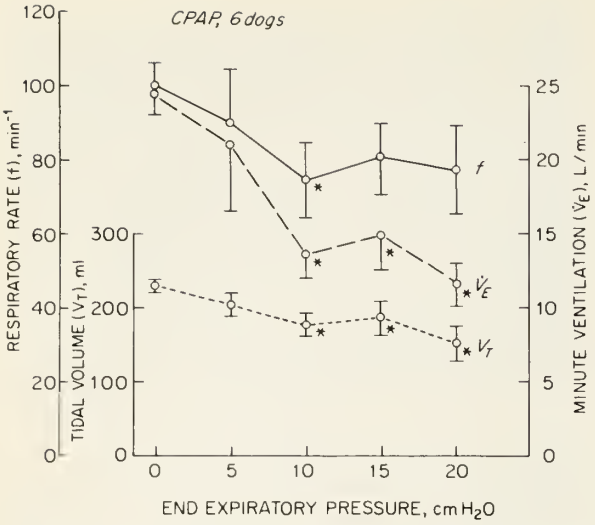

Figure 12.—Mean and standard error of respiratory rate (f), tidal volume (V_T) and minute ventilation (V_E) at 0, 5, 10, 15 and 20 cm of water of CPAP during spontaneous breathing (significant changes as in Figure 11).

intrapulmonary shunts (that is, a decrease in the fraction of total cardiac output, $\dot{Q}_s/\dot{Q}_t$, passing through the lungs without gas exchange for oxygen). There are minor differences between the effects of PEEP and CPAP.

Figure 11C shows a significant fall in cardiac output at the highest levels of PEEP, a complication frequently reported. In contrast to PEEP, there was no significant change in cardiac output during increments of CPAP, resulting in a significantly higher cardiac output at the highest end-expiratory pressure than during PEEP. This difference is probably because mean airway pressure in spontaneously breathing subjects is lower than during mechanical or positive pressure ventilation. This occurs even at the same end-expiratory pressure,[75] resulting in difference in mean intrathoracic pressure, venous return, and cardiac output.

Figure 11D shows essentially the same effects on oxygen delivery, which depends on both cardiac output and arterial oxygen content. Decreased cardiac output seems to have had more effect than improved arterial oxygen content during PEEP.

Figure 11E shows mean P_{VO_2} at various levels of end-expiratory pressure. Two critical points are noted. First, mixed venous oxygen tension rose with increasing end-expiratory pressure during both PEEP and CPAP, suggesting that both maneuvers improved tissue oxygenation,[81] a point not well-established previously. During PEEP, the mean control value of 27.5, approaching the level critical in development of anaerobiasis and lactic acidosis,[82,83] rose to a mean of 34, significantly above the original level. The second important point is that the increase in P_{VO_2} during CPAP was even greater, since arterial oxygenation improved without a decrease in cardiac output. Thus CPAP, when applicable, results in greater improvement in tissue oxygen tensions than does PEEP at the same end-expiratory pressure. One implication of this is that during CPAP lower concentrations of oxygen or less pressure may be necessary than during PEEP.

Because of the difference in hemodynamic responses, CPAP might be preferable to PEEP. However, significant differences in ventilatory responses were also noted. Figure 11F shows that mean arterial carbon dioxide pressure (P_{ACO_2}) remained constant during PEEP with constant mechanical ventilation, as expected. However, P_{ACO_2} rose during CPAP at every level of increased end-expiratory pressure, presumably because of the external ventilatory load, which can decrease ventilation and cause hypercapnea. The increased work of breathing could be both inspiratory and expiratory, as expiration is often active rather than passive during CPAP. Furthermore, the increase in lung volume associated with increased expiratory pressure may result in decreased compliance and increased inspiratory work of breathing. Therefore, although CPAP seems to be preferable to PEEP because of a significant difference in hemodynamic responses, ventilatory responses are a potential drawback.

To examine further the mechanism of the ventilatory response during CPAP, we studied effects of 15 cm of water of CPAP on respiratory frequency (f), tidal volume (V_T) and minute ventilation (V_E) of six dogs (Figure 12). Respiratory frequency was extremely high at the onset; it dropped during CPAP, but not significantly. Tidal volume decreased slightly. The minute ventilation (the product of frequency and tidal volume) fell significantly during CPAP, accounting for the increase in P_{ACO_2}.

In order to block afferent impulses of pulmonary reflexes (which might affect ventilation), these measurements were done before and after cooling the cervical vagi to 2°C. Figure 13 shows that blocking the vagus resulted in a change in breathing pattern from rapid shallow breathing to slow deep breathing. This was probably caused by blocking afferent impulses from stretch recep-

tors in the lung,[84] which may be abnormally active in abnormal situations such as this model of ARDS. Total $\dot{V}_E$ also decreased. However, Figure 14 shows that vagal cooling resulted in a very significant decrease in $PaCO_2$ during CPAP. This can be attributed to the decrease in f, so that the V_T, no longer limited by high flow rates, increases.[84] Despite a decrease in total minute ventilation, $PaCO_2$ improved, indicating that a decrease in dead space ventilation with lowering of f was a major factor.

These data from animal studies suggest that (1) PEEP and CPAP can improve tissue oxygenation when used under appropriate circumstances, (2) CPAP is potentially the more effective of the two at any given level of end-expiratory pressure and (3) CPAP can also cause stimulation of lung reflexes, an abnormal breathing pattern and significant hypercapnea. Perhaps these data will have some significant implications for therapy of ARDS in humans.

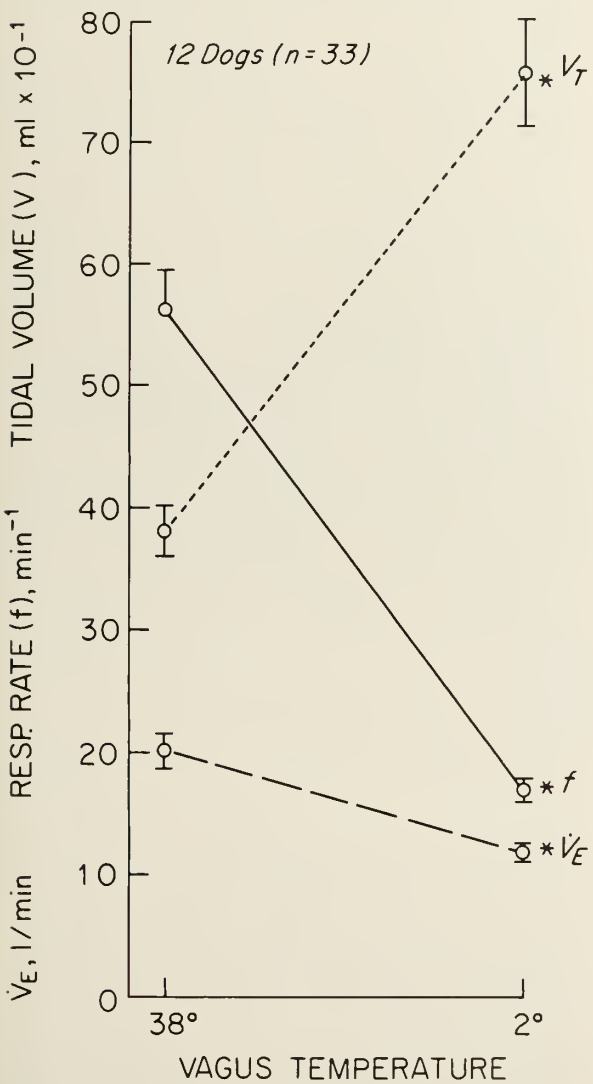

Figure 13.—Mean respiratory rates (f), tidal volumes (V_T) and minute ventilations (V_E) (±SEM) of spontaneously breathing dogs on 15 cm of water of CPAP before and after cooling both cervical vagi to block afferent limbs of pulmonary reflexes.

* = significant changes.

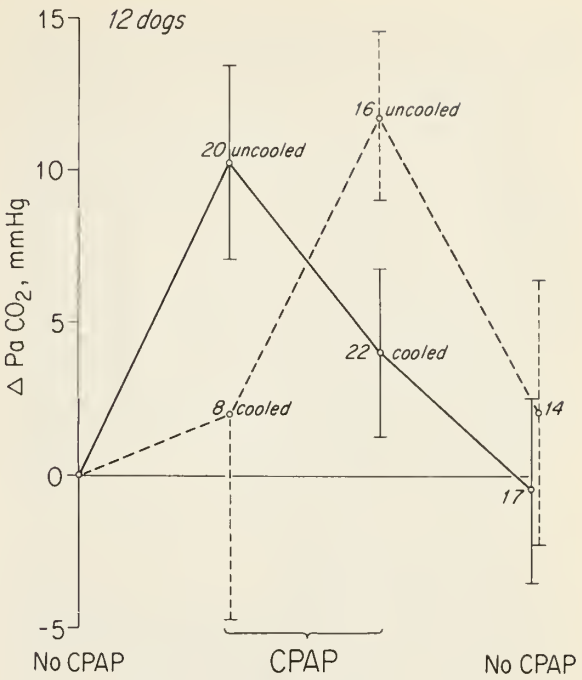

Figure 14.—Mean changes in $PaCO_2$ (±SEM) of 12 spontaneously breathing dogs with and without 15 cm of water of CPAP, and with and without cervical vagal cold blockade (cooled versus uncooled). The order of normal and vagal blockade was alternated in two groups. The number of measurements for each mean is shown.

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Cigarette Smoking and Early Menopause

WE STARTED LOOKING at our data for one reason or another on menopause and at the same time we were looking at our data on smoking. So we looked at the two of them combined and, lo and behold, we found that there is a striking relationship between smoking and age of menopause. A summary of data . . . shows that women who smoke tend to have an earlier menopause, and the more a woman smokes the earlier the menopause. At age 48-49, for example, among 195 never-smokers only 26 percent were postmenopausal at that time; among heavy smokers, almost twice as many, 46 percent, were postmenopausal; at 50-51, 56 percent of never-smokers, 79 percent of heavy smokers were postmenopausal.

—HERSCHEL JICK, MD, *Boston*

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Refer to: Venereal aspects of gastroenterology—Medical Staff Conference, University of California San Francisco. West J Med 130:236-246, Mar 1979

Venereal Aspects of Gastroenterology

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *We have asked Dr. Robert Owen from the gastroenterology division at San Francisco Veterans Administration Medical Center to discuss some aspects of venereal gastroenterology, which are seen frequently here at the University of California and in many other clinics in San Francisco. He will be joined by two prominent people from San Francisco with wide experience in this area: Dr. Selma Dritz, who is medical epidemiologist with the San Francisco Public Health Department, and Dr. Charles Wibbelsman, who is chief of the Division of Venereal Disease Control in San Francisco.† Dr. Owen will begin with an overview of the topic of venereal gastroenterology.*

DR. OWEN:‡ In this conference we will discuss several venereal aspects of gastroenterology, concentrating on sexual transmission of enteric diseases and intestinal presentation of venereal diseases. There are always problems for both patients and physicians dealing with human sexuality. It is not an easy subject for either group, but it is critical that sexual problems be dealt with in a straightforward manner if we are to be effective. Patients always want one to think well of them and they will not tell an interviewer what they think he or she does not want to hear. Consequently in most cases one only obtains as much history as one is prepared to accept. It is important, therefore, when taking a history to understand the full range of the problem to be encountered so as to ask appropriate questions. Sometimes physicians are afraid to offend patients by asking questions that imply conduct that could be considered unacceptable or that may not be relevant. Today, we are trying to present sufficient background so that one will be familiar with the appropriate questions. Neither a patient nor medicine is well served when significant diagnoses are missed because the diagnoses were not considered.

Venereal Transmission of Enteric Disease

All orifices of the body are highly endowed with nerve endings. Evolutionarily this has proven useful; it is necessary to know if a bug is crawling in one's ear or nostrils, and to ascertain whether one is passing gas, liquid or solid material through

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the anal sphincter. The human body is often used in ways scarcely predictable from our evolutionary history. It is unlikely that the vocal cords evolved for singing grand opera. It is at least as unlikely that the human rectum evolved for sexual function, but it is often used that way. Mankind seems to be very imaginative in its demands upon the human body. At present, widely available sexual manuals refer to all orifices as erotic areas, regardless of their other functions. It is unclear whether erotic contacts involving orifices other than the genitals are now more common, but certainly we are more aware of them. It may be that our threshold of awareness has changed. Roman, Greek and Chinese literature indicate that there are no new permutations and combinations of anatomical parts. Venereal transmission of rectal herpes was reported in the French literature more than 200 years ago, but there were few recent reports until 1976.[1] The ability to discuss sexual issues has increased, which is to our advantage in making timely diagnoses.

In metropolitan areas, with relative anonymity and the confrontation of varied cultures, there may be a greater incidence of sexually related gastrointestinal disease than in rural areas. Or it may be that because of anonymity sexual problems are presented as what they are rather than as something else. In California because sexual activity—including homosexuality—between consenting adults is not illegal, material may be brought to physicians' attention that would be reinterpreted and presented with other explanations under other judicial circumstances. In Helsinki, Finland, the reported incidence of homosexually related syphilis cases was 2 percent when there was a 2-to-15 year prison penalty for homosexuality.[2] After homosexual expression between consenting adults was legalized, up to 50 percent of patients with genital syphilis reported homosexual contacts. Patients clearly are not going to present material that could put them in legal jeopardy. One may hear about things in California that would not be heard in other areas where laws are different.

The gay bowel syndrome is a designation that has recently appeared in medical literature to describe multiple and recurrent bacterial, protozoal and viral infection from oral-anal exposure, or rectal trauma that may be associated with anal intercourse.[3,4] It is probably not a good term if it restricts our thinking regarding the sexual basis for intestinal disease to homosexuals. Oral, genital and anal erotic behavior is obviously found in heterosexuals, as well. In a prospective study of patients presenting for family planning counseling, for Papanicolaou smears and for a variety of gynecological problems, 526 consecutive women were interviewed regarding their previous experience with anal erotic behavior including anal intercourse. Of these women, 25 percent indicated that at some time they had used this as a means of sexual satisfaction and 8 percent regularly included such behavior, including anilingus, as a means of stimulation.[5] These heterosexual patients could also be subject to the same range of diseases that we generally think of as the gay bowel syndrome. Physicians with large numbers of homosexuals included in their practices have become sensitized to the likelihood of venereal transmission of multiple enteric organisms. Venereal transmission of enteric pathogens may occur much more frequently in heterosexual men and women than is recognized.

The recognition of the female rectum as a reservoir of asymptomatic gonorrhea was long obscured by the blind spot of physicians who refused to recognize that anal intercouse was occurring as a birth control measure, as an alternative to vaginal patulousness, during menstruation or for variation. Rectal gonorrhea was desexualized and considered secondary to lymphatic spread or use of infected douche handles or nozzles, or caused by anterior-posterior wiping after urination. Physicians arrived at some remarkable explanations rather than approach the obvious.[6] No one asked the right questions and no one got the right answers.

Homosexual men do have a high incidence of sexually related intestinal disease, perhaps because there is little societal pressure towards monogamy even where private homosexual behavior is legal. Their numbers of contacts may also be greater because of high mobility in jobs favored by persons without domestic attachment—the merchant marine, long distance trucking, airlines, traveling sales, entertainment or sports. In all large cities, and many small ones, there are public bath houses where naked, anonymous persons may engage in repeated sexual contacts, having statistically a much greater chance of exposure to disease. As numbers of contacts increase, particularly with those who also have had large numbers of contacts, chances of transmission of enteric or venereal disease approach certainty. In San Francisco the Department of Public Health has maintained diagnostic booths for venereal diseases in

public baths, some of which have capacities of 500 to 1,000 and where, despite lots of soap and water, there have been high rates of disease transmission. Dr. Wibbelsman will discuss this later.

Few women appear to frequent either homosexual or heterosexual bath houses, perhaps because sexual function is not so external or superficial for women as for men. At any rate, venereal and enteric diseases appear to occur very infrequently in homosexual women—the incidences are lower, in fact, than in heterosexual women or men, and much lower than in homosexual men. If nothing else, lesbianism does not seem to be bad for one's health.[7]

During sexual encounters, judgment is often curtailed and magical or omnipotent thinking occurs. Persons presume that they will not be the ones to contract venereal disease. As children we learn that fecal organisms can transmit disease but it often seems everyone forgot. Amebiasis,[8] shigellosis[9,10] giardiasis,[11,12] salmonellosis including typhoid,[13] and hepatitis[14] appear to be spread by venereal transmission. Many types of behavior seem reasonable during the height of passion or when a person is intoxicated but may seem foolish the next day. Patients may be reluctant to be candid about their own behavior, unless one broaches the subject when taking the history.

With recurrent attempts to limit vocational opportunities or abridge the civil rights of homosexuals—as with the recently defeated Briggs initiative in California—patients may become more hesitant to be candid for fear that their sexual orientation will be recorded. Their charts, after all, are legal documents which are subject to subpoena and, unfortunately, to casual reading by medical and clerical personnel. Often the lowest clerical positions in hospitals are in record rooms, and some of the least trained and least qualified people handle the charts. We must decide whether it is more to a patient's benefit to record sexual preference in our records to alert other health personnel to possible sexually related disorders, or to omit such information to guard against blackmail and possible job loss for the patient.

Dr. Dritz will review the experience in San Francisco with the venereal transmission of the enteric diseases—a subject that came strongly to my awareness when Dr. Al Hurwitz and I studied the cases of several patients who had multiple and recurrent intestinal parasites, including amoebae and Giardia.[12] We first thought we were seeing treatment failure or drug resistance when we continued to culture amoebae. Noticing that different amoebae were being cultured, we realized we were seeing reinfection rather than drug failure. These patients had no history of travel out of San Francisco and from earlier training one would not have strongly considered amebiasis in an initial differential diagnosis. These patients were not cleared of enteric parasites until careful sexual history indicated the apparent mode of reinfection. We pursuaded them, by explaining what was happening, to interrupt at least temporarily their usual mode of behavior which involved anilingus; and infections abated. In discussion with Dr. Dritz we learned that our observation reflected common epidemiologic patterns of enteric disease transmission in San Francisco.

Epidemiology of Venereally Transmitted Enteric Disease

DR. DRITZ:* In San Francisco the epidemiology of sexually transmitted enteric diseases seems to be related to both political and social changes in the city. In 1974 a change in political atmosphere in the city made it apparent that legal pressures on the homosexual community would be eased. This was accompanied by an increase in the population of homosexuals in two particular areas of the city. Within six months we noticed the beginning of a rapid rise in reported cases of amebiasis, shigellosis and viral hepatitis. Polling the physicians who made these reports, we learned that most of their cases were in men between the ages of 20 and 40, and that most of these men were residents, employees or habitues of the gay communities, or gave histories of frequent or varied sexual activity with male partners. In order to assure ourselves that this was not an artifact, we analyzed our data for the preceding ten years.[15] As background, let me describe the demography of the city.

San Francisco has a population of approximately 660,000. Of these, two thirds are white, of which a fourth are of Spanish ethnic origin. Of the remaining third, half are black, about a third are Chinese or Japanese, and the rest include East Indian, American Indian, Burmese, Indonesian, Samoan, Korean, Polynesian, Philippine and Arabic groups. Male and female populations are approximately equal in the age groups under 50 years, with a 25 percent preponderance of women

*Selma K. Dritz, MD, Assistant Director, Bureau of Disease Control, San Francisco Department of Public Health.

over that age. We feel that whatever sexual skew may exist in our reports of disease incidence, it is not due to a large discrepancy of age or sex in the population distribution. Although perhaps only a third to a half of all reportable diseases are actually reported in San Francisco, we believe that this percentage is a constant factor, and does not appreciably affect our year-by-year study. Some of our morbidity data *are* statistically skewed due to an intense epidemiological effort by interested physicians whose practices include numerous patients who have adopted what are now called alternate life-styles. The cases of amebiasis, salmonellosis, shigellosis and hepatitis B shown in Tables 1, 2 and 3 are all laboratory confirmed, with the exception that before 1974, when the hepatitis-associated antigen (HAA) test became generally available, hepatitis B diagnoses were based on a history of probable parenteral contamination. Diagnoses of hepatitis A were accepted on the physicians' clinical impression, if tests were negative for hepatitis B antigen.

In 1967 and 1968 we had an influx of about 100,000 "flower children" into the Haight-Ashbury District, followed by an increase in cases of

TABLE 1.—*Reported Cases of Selected Diseases, San Francisco Department of Public Health*

Year	Amebiasis	Shigellosis	Hepatitis A	Hepatitis B	Hepatitis-Type Undetermined*
1964	8	76	150	25	...
1965	5	81	181	77	...
1966	13	17	204	84	...
1967† ...	24	69	552	203	...
1968† ...	21	48	819	388	...
1969	17	144	651	285	...
1970	23	85	723	182	...
1971	23	159	767	123	...
1972	8	254	542	86	...
1973	15	208	696	161	...
1974	10	189	480	144	...
1975‡ ...	78	346	647	241	22
1976‡ ...	101	602	912	334	63
1977‡ ...	103	325	690	351	115

*Defined mid-1974.
†Haight-Ashbury period.
‡Venereal transmission recognized.

TABLE 2.—*Case Incidence in San Francisco Per 100,000 Population By Age and Sex*

Age (Years)	Sex	Population* (1,000's)	Shigellosis 1969	Shigellosis 1975	Shigellosis 1976	Shigellosis 1977	Salmonellosis† 1977	Amebiasis 1969‡	Amebiasis 1975	Amebiasis 1976	Amebiasis 1977
<20	M	88.4	43	31	50	26	25	..	2	2	3
	F	89.8	56	22	30	12	19	..	0	0	3
20-29	M	57.2	21	238	390	215	25	..	70	80	71
	F	58.1	14	29	60	26	22	..	3	2	2
30-39	M	44.1	20	188	361	197	7	..	48	93	70
	F	41.1	70	29	29	29	10	..	2	0	5
40-49	M	36.0	17	69	78	13	19	..	17	8	11
	F	36.4	3	3	3	3	11	..	3	0	0
>50	M	94.6	2	8	13	7	7	..	2	4	1
	F	121.8	2	7	3	4	9	..	2	1	1
Number of Cases			144	346	602	325	113	17	78	101	103

*Estimated, July 1975.
†For comparison with shigellosis rates.
‡Age/sex distribution not available for 1969.

TABLE 3.—*Case Incidence in San Francisco Per 100,000 Population By Age and Sex*

Age (Years)	Sex	Population* (1,000's)	Hepatitis A 1969	Hepatitis A 1975	Hepatitis A 1976	Hepatitis A 1977	Hepatitis B 1969	Hepatitis B 1975	Hepatitis B 1976	Hepatitis B 1977	Hepatitis-Type† Undetermined 1977
<20	M	88.4	88	18	32	40	58	10	9	9	3
	F	89.8	96	16	17	20	30	1	10	8	3
20-29	M	57.2	390	635	906	573	248	187	241	302	110
	F	58.1	251	131	172	91	72	38	45	59	17
30-39	M	44.1	150	259	481	283	23	98	107	186	54
	F	41.1	31	49	58	63	10	12	7	12	2
40-49	M	36.0	61	42	125	64	8	28	30	31	8
	F	36.4	5	14	36	19	8	3	11	11	3
>50	M	94.6	10	10	17	11	4	10	14	10	1
	F	121.8	7	9	11	4	1	5	5	3	1
Number of Cases			651	647	912	690	285	241	334	351	115

*Estimated, July 1975.
†Age/sex rates not available prior to 1977.

TABLE 4.—*Antibiotic Resistance Patterns of Shigella flexneri Isolated From 37 Cultures From Patients at San Francisco General Hospital—1978*

Medication	*Percent Resistance*
Cephalothin	0
Gentamicin	0
Kanamycin	0
Polymyxin B and E	0
Tobramycin	0
Trimethoprim/sulfamethoxazole	0
Amikacin	3
Chloramphenicol	5
Carbenicillin	16
Ampicillin	22
Tetracycline	90

hepatitis A and B and some increase in cases of amebiasis (Table 1). Most of the patients with amebiasis gave a history of having been in Nepal or India, or in Mexico looking for peyote or marijuana. We know that some of the histories were not reliable, and a large number of the patients disappeared from medical follow-up. Hepatitis A probably increased due to the unsanitary, overcrowded, nonconformist characteristics of commune living in the Haight of that period. By patients' histories, most of the hepatitis B was probably needle-transmitted and a direct result of the use of street drugs. After 1968 societal pressures were applied, and the Haight-Ashbury culture dispersed. Many of the young people migrated to Southern California, and San Francisco retained chiefly a criminal hard-drug element. The amebiasis incidence remained slightly elevated at 10 to 20 cases per year—most of the patients giving a history of probable exposure to unsanitary conditions during travel in underdeveloped countries. Shigellosis incidence began a slow rise; I cannot explain why we did not note that in 1967 and 1968. Perhaps it was due to inadequate reporting, or perhaps most of the cases of diarrhea of minor character were treated successfully without resorting to laboratory diagnosis. Hepatitis A incidence remained high, although somewhat below the level it had reached in 1968; hepatitis B dropped slightly.

In mid-1974 the gay community began to expand rapidly from an estimated population of between 30,000 and 40,000 to what city officials now estimate as about 120,000; other estimates range down to 70,000. I use about 100,000 as a reasonable compromise figure. San Francisco has a total population of 660,000 persons with roughly 300,000 males; in this population are about 100,000 predominantly homosexual men and an unknown number of homosexual women. As the gay community expanded, the reported incidence of amebiasis jumped from 10 cases in 1974, to 101 in 1976 and 103 in 1977. Reports of cases of shigellosis increased almost geometrically, with a comparable increase in both types of hepatitis.

We began to publicize the outbreak to the gay community and to physicians in the city. At least partly because of heightened awareness of venereal transmission of enteric disease and specific treatment by physicians, we saw in 1977 a 30 percent to 40 percent drop in shigellosis and hepatitis A incidence. The incidence of hepatitis B has not dropped appreciably. We believe that much of the current hepatitis B incidence may be due to transmission of the virus during sexual contact. Saliva, semen, urine and blood have all been identified as carriers of the hepatitis B antigen,[16,17] and it would require only a very small break in oral, genital or anal mucosa for a virus-contaminated body fluid to become "parenterally injected" during sexual intercourse.

Tables 2 and 3 show the current preponderance of males with enteric infection despite the almost equal division in the population of men and women under 50 years of age. I used 1969 for a base year for data because it is between the 1967 Haight-Ashbury summer and the 1974 expansion of the gay community. In 1969 shigellosis incidence was relatively equal in both sexes. The male/female ratios of shigellosis incidence per 100,000 population changed enormously in 1975 and thereafter, with ratios of 238/29 for 1975, 390/60 for 1976 and 215/26 for 1977 in ages 20 through 29 (Table 2). This difference in rates is too great to be explained by a failure of physicians to diagnose cases in women. In contrast to shigellosis, the incidence of salmonellosis cases remained relatively equal in the sexes throughout these years. We had no outbreak of salmonellosis in the gay community. This may possibly be due to differences in infective dose. With salmonella, a dose of 10^4 to 10^6 organisms is needed to produce overt disease, while with shigella, 10 to 100 organisms are sufficient. As with shigellosis, there also was a great disparity in male/female ratios of amebiasis in the ages 20 through 39 (see Table 2). Hepatitis also shows a preponderance of males in the sexually most active age groups (Table 3). We identify perhaps one or two food handlers per month as carriers of these enteric pathogens and have not identified food establishments or water

supplies as sources of multiple-case outbreaks. In fact, two cases of food handlers in whom tests were positive for Salmonella typhosa appeared to have represented venereal transmission of infection.[13]

Therapy for shigellosis may be a problem, even though various antibiotics are available. In 37 cultures of Shigella flexneri from patients at San Francisco General Hospital, on whom antibiograms were done during the first half of 1978, the resistance patterns shown in Table 4 were found. Physicians in San Francisco report using ampicillin and trimethoprim/sulfamethoxazole most frequently when antibiotics are deemed necessary. For amebiasis, metronidazole seems to be the treatment of choice of clinics and physicians in the city, and diiodohydroxyquin is used for the occasional patients who cannot tolerate the enteric side effects of metronidazole. Physicians report finding some asymptomatic carriers of Entamoeba histolytica among named sexual contacts of their patients.

Hepatitis A and B are difficult problems for therapy, with general supportive measures the chief resource at this time. Immune serum globulin is of limited use for passive protection of contacts, its effectiveness circumscribed by time limitations and by the fact that while it may suppress symptoms of the disease, it does not appear to prevent viremia and infectivity of the contact. The new hepatitis B immune globulin (HBIG) is prohibitively expensive at present for a general preventive passive immunization program and seems to delay rather than abort infection. We need an effective and readily available, inexpensive active vaccine for both types of the hepatitis virus.

DR. OWEN: Patients with venereal exposure to a variety of partners can present with multiple enteric pathogens simultaneously or sequentially.[18] When oral-anal venereal transmission of amebiasis or shigellosis is identified, it is prudent to look for giardiasis and hepatitis as well. Conversely, in patients without a history of recent travel or immunodeficiency, diagnosis of multiple enteric pathogens suggests venereal transmission.[19] In such patients intestinal symptoms may represent the summation of the effects of different organisms. Consequently one or more parasites may be found in follow-up stool examinations after elimination of symptoms following treatment.[12] Endolimax nana, an ameba not usually considered pathogenic, has been associated with symptoms responding to administration of metronidazole.[20] Infection with such nonpathogens may result in symptoms when rectal trauma, which I will discuss below, permits noninvasive amebae to enter the mucosa. Granulomatous response to cutaneous amebae may resemble anogenital condylomata[21] or even carcinoma.[22] Trophozoites should be looked for in biopsy specimens before radical surgical excision.

Gastrointestinal Presentations of Venereal Disease

DR. WIBBELSMAN:* Dr. Dritz presented an overview of enteric disease trends in San Francisco and conflicting estimates of the gay population which range between 100,000 and 200,000 in a city of almost 700,000 population. There are 72,000 patient visits a year to the San Francisco Department of Public Health's City (venereal disease) Clinic which is open five days a week, eight hours a day. My impression is that 60 percent to 80 percent of these patients are gay men. One should be aware of the following facts: San Francisco leads the United States in reported cases of primary and secondary syphilis in cities of 200,000 and more population with a rate of 123.9 per 100,000 population (1977). San Francisco was fourth in gonorrhea incidence in 1977 with 2,352.1 cases of gonorrhea per 100,000 population, surpassed by Atlanta, Baltimore and Washington, D.C. Most of the reported syphilis and gonorrhea diagnoses in San Francisco are made in our facility.

Gonorrhea

In 1973 the City Clinic reported 2,492 cases of gonococcal proctitis in males which doubled by 1976 to 4,932, reflecting both an enlarging gay population and increased disease transmission. In 1977 at the City Clinic 14,013 cases of gonorrhea were diagnosed, of these 4,655 were proctitis and 334 pharyngitis. Gonococcal infections of both the pharynx[6,23] and rectum[6,24] are often asymptomatic but the pharynx appears to be a much less significant reservoir for transmission than the rectum.

What makes venereal disease an epidemic in San Francisco? There are three main factors: anonymity, increased opportunities for sexual activity and asymptomaticity. The high rate of gono-

*Charles J. Wibbelsman, MD, Chief, Division of Venereal Disease Control, San Francisco Department of Public Health (at the time of this conference).

coccal proctitis and the percentage of infected persons being asymptomatic (as high as 80 percent) indeed are significant contributing factors. Dr. Owen alluded to Department of Public Health screening for venereal disease in bath houses. We also go out to the street corners with our mobile van. At one site in San Francisco in an hour 50 asymptomatic men volunteered for a checkup. In ten of these men rectal cultures were positive for gonorrhea. When one considers that 20 percent of this sample had rectal gonorrhea and did not know it, we get some insight as to why San Francisco has such a high rate of gonorrhea.

Those that do have symptoms with rectal gonorrhea give a fairly consistent history, even though their signs and symptoms are nonspecific.[24] Persons with rectal gonorrhea often notice strands of white mucus on their stool, and may complain of one or all of the following symptoms: flatus, constipation and rectal itching. Although any condition that causes chronic moisture in the rectal area can cause itching, my clinical impression is that the discharge associated with a rectal infection may be particularly capable of causing pruritus. We do not treat all patients who come into the clinic with only nonspecific rectal complaints, but if a gay man who is quite active sexually, especially one who has had rectal gonorrhea in the past and has no history of chronic colitis, comes in and states "I have mucus in my stool," he probably has rectal gonorrhea. Such patients may say that they have been in a bath house and do not know their contacts. They do not know if the person they have had sex with may have been diagnosed with gonococcal urethritis subsequently so that they could have been infected, but they do know that they have mucus in their stool. In such situations we take cultures for gonorrhea and treat for gonoccoccal proctitis on epidemiologic grounds. In at least half of such patients the diagnosis of gonorrhea is confirmed.

Every man in whom the diagnosis of gonococcal urethritis is made in the City Clinic is interviewed by an epidemiologist; these are the only persons with gonorrhea whom we interview because their infected contacts will often be asymptomatic and not aware of the need for treatment. Of those persons named as rectal contacts to gonococcal urethritis in 1977, rectal cultures were positive in 46 percent. That is quite significant. In contrast, in those persons with *only* pharyngeal contact to gonococcal urethritis, pharyngeal cultures were positive in less than 9 percent of cases. Major reasons for the epidemic of gonorrhea are the susceptibility of the rectal mucosa to an infected penis and the asymptomaticity of rectal gonorrhea.[6] Contacts of rectal carriers are not traced because of economic limitations and because their symptoms of urethritis will lead them to treatment.

Syphilis

When we consider primary syphilis, some of the same epidemiologic factors prevail. In 1977 there were 364 primary and 370 secondary cases of syphilis diagnosed in the City Clinic. Why did we see nearly 400 cases of secondary syphilis? Were these people unaware that they had a primary lesion? If it was rectal they may well not have known. Symptoms of a primary rectal chancre may be quite variable and are totally nonspecific.[25,26] Many patients either take no notice of enlargement of inguinal nodes or may not necessarily relate it to syphilis or other infectious processes, such as herpes, that can also cause inguinal adenopathy.[11] Therefore, in syphilis—much as in gonorrhea—one of the reasons that we may have not diagnosed or seen many of these primary lesions is because of asymptomaticity of rectal lesions.

The patient load at the City Clinic is quite heavy: as many as 425 people in one day. We do not have the time to use an anoscope or a proctoscope in every case in which there is a suspicion of venereal disease. Instead we are restricted to a limited physicial examination including visualization of the perianal area, and diagnosis, treatment and epidemiology of syphilis and gonorrhea. Many of the primary lesions of syphilis that we see are perianal, although undoubtedly there are a significant number of primary lesions inside the rectum that we do not diagnose because they cannot be seen in a perianal examination. If we had the time, staff and budget, we would increase the number of primary diagnoses by using an anoscope in every patient exposed to a man having syphilis, especially those patients who have inguinal adenopathy without a visible external lesion. Most of our primary diagnoses are made by positive findings on darkfield examination, which is a critical evaluation in early syphilis. Occasionally, in a person with an early primary lesion that is darkfield positive, a Venereal Disease Research Laboratory (VDRL) test may be nonreactive and a fluorescent treponemal antibody absorption test (FTA-ABS) negative. The only diagnostic laboratory tool is a positive darkfield examination. This

emphasizes the inadequacy of a single VDRL test for a patient recently exposed to syphilis. One must see the patient at periodic intervals from the date of contact for up to three months which corresponds to the maximum 90-day incubation to detect seroconversion. Our policy in the City Clinic is to offer epidemiologic (prophylactic) treatment to all persons exposed to syphilis in the previous 90 days as opposed to following these cases serologically, waiting for syphilis to develop and then looking for contacts.

Treatment of Gonorrhea and Syphilis

The Center for Disease Control's recommendations for the treatment of syphilis are followed at the City Clinic.[27] Primary and secondary syphilis are treated with 2,400,000 units of benzathine penicillin G given by intramuscular injection. In early latent cases, patients receive the same treatment each week for two weeks; in late latent cases, for three weeks, and in cases of neurosyphilis, for four weeks. Patients allergic to penicillin are given tetracycline or erythromycin, 750 mg by mouth every six hours for ten days to a total of 30 grams. For patients with late latent or neurosyphilis treatment time is doubled for a total dose of 60 grams.

In treatment of rectal and pharyngeal gonorrhea, our first choice is aqueous procaine penicillin G (APPG), 4.8 million units given intramuscularly, and a gram of probenecid (Benemid) by mouth.[28] Administration of APPG, unlike other modes of treatment, is acceptable treatment for gonorrhea of all sites of infection: pharyngeal, cervical, urethral or rectal. Although ampicillin has been advocated for treatment of pharyngeal gonorrhea,[29] we have had a better cure rate for rectal and pharyngeal gonorrhea using APPG, and have seen several ampicillin failures in the treatment of rectal gonorrhea. Some physicians in San Francisco do not use APPG to treat gonorrhea; their reasons and justification for using orally given antibiotics are the risks associated with APPG. Patients indeed can have serious allergic reactions; also, procaine reactions can be quite disturbing because of unexpected symptoms such as hallucinations. The most severe procaine reaction I have seen was a grand mal seizure. Perhaps these risks of an acute reaction to penicillin or procaine are the reasons physicians in those treatment settings without resuscitation equipment available or without adequately trained staff may hesitate to use APPG. We have observed that some physicians whose practice is heavily weighted with homosexual males will use ampicillin at higher doses, such as 4.5 grams to treat rectal gonorrhea, claiming that this is effective. Even if gonorrhea is eliminated, this regimen lacks a major patient advantage of aqueous penicillin G, that is, its documented abortive effect on incubating syphilis.

Last year nearly 1,450 cases of infectious syphilis were diagnosed in the City Clinic, 95 percent in men naming other men as contacts. However, I have noticed at our clinic that in those homosexual patients with a high recidivism rate for gonorrhea and frequent treatment with APPG, syphilis is not found to be present. If a patient has gonorrhea and is treated with APPG, one can be assured of aborting incubating syphilis. That is why we consider APPG the drug of choice for treating gonorrhea in nonallergic male patients. A small number of patients in whom gonorrhea is diagnosed and in whom results of a VDRL test are negative, have a pronounced reaction consistent with a Herxheimer reaction after treatment with APPG. If this is genuine, it would be diagnostic of syphilis. Now that we are forced by budget limitations to use ampicillin to treat all men with gonococcal urethritis, we may learn whether ampicillin has any effect on incubating syphilis.

Although tetracycline can provide adequate therapy for gonorrhea, one must recognize that patient compliance is of the utmost importance for successful outcome. If one dispenses to a patient a package of 4½-days dosage of tetracycline pills to treat gonorrhea, there is always the risk he will lose the pills, share the pills with lovers or forget to take them. However, assuming excellent patient compliance, tetracycline does work quite effectively in pharyngeal, urethral, cervical and rectal gonorrhea. In some women treated for cervical gonorrhea with tetracycline, yeast infection may develop.

Spectinomycin has the advantage of single intramuscular dose therapy for gonorrhea, but it is expensive and has no effect on syphilis because it is not spirocheticidal. Administration of 2 grams of spectinomycin does work well for rectal, urethral and cervical but not pharyngeal gonorrhea. Approximately 200 cases of the penicillinase producing Neisseria gonorrhea (PPNG strain) now have been reported in the United States, including 15 in San Francisco. We successfully treated a pharyngeal contact to a PPNG strain with 4 grams of spectinomycin as per the Center for Disease

Control's recommendation. Otherwise, spectinomycin is not recommended to treat pharyngeal gonorrhea—and, to reiterate, it has no effect on incubating syphilis.

An important consideration when one is treating someone for gonococcal proctitis, cervicitis or pharyngitis, is to obtain a follow-up culture for test of cure. In all cases of treatment failure to APPG, when there has been no reexposure, a regimen of tetracycline is used. If the second test of cure is positive without reexposure, therapy with erythromycin may be used although our experience with this drug as the second choice for a penicillin treatment failure after tetracycline has not been impressive. Spectinomycin probably should be the next course of therapy after penicillin and tetracycline treatment failures. I have yet to see a failure of spectinomycin to cure rectal gonorrhea. Usually we use 2 grams, occasionally we may have to use 4 grams if the patient is very uncomfortable, suggesting massive infection.

DR. OWEN: There are a couple of additional points I want to make about the venereal diseases. One may ask what will be seen upon proctoscopy in gonorrhea. As one may guess from the number of asymptomatic patients,[6] the commonest appearance is normal mucosa.[24] Without a culture, one cannot make the diagnosis. When there are symptoms with either pharyngeal or rectal gonorrhea, they seem to represent host factors or coinfection with another organism, since Neisseria gonorrhea alone is not sufficient for either symptoms or signs. Mechanically traumatizing the anal mucosa may allow bacteria to enter.

When proctoscopy shows abnormalities, erythema and surface mucus extend up into the rectum only about 8 cm and stop abruptly. This sharp delimitation of mucosal abnormality is consistent with but not diagnostic of gonorrhea. Unfortunately there is no more specific presentation. Rectal cultures are most effective when obtained through a proctoscope, but the diagnosis of rectal gonorrhea can be made with blind swabs 96 percent of the time.[30] Enter the anal canal with the swab about an inch, move it side to side and remove. If the swab is grossly contaminated with feces, discard and repeat. The problem with culturing gonorrhea is usually not how one obtains the specimen, but whether one keeps it warm on its way to being cultured and whether it is planted onto appropriate media, such as Thayer-Martin medium which suppresses most bacteria other than Neisseria. With symptomatic pharyngitis, one will not be able to diagnose gonorrhea with the routine throat culture which is selective for beta Streptococcus.

With syphilis one may see a chancre within the anal canal or rectum, and it may even resemble carcinoma.[31] There have been patients in whom anal resection was done, or nearly done, for a superinfected chancre with an inflammatory reaction around it. Unlike penile chancres, rectal chancres can be painful.[26] Because signs and symptoms are nonspecific, darkfield examination, biopsy with stains for spirochetes, or repeated serologies are necessary to confirm a diagnosis.

Anorectal Herpes Infection

The next topic is the rectal presentation of herpes. There are two types of herpes simplex, I and II. We usually think of type I as occurring above the belt and type II below the belt, but the territories are not exclusive. Particularly in younger patients, there may be type I genital or rectal lesions in a third of cases, probably relating to initial orogenital exposure. Waugh reported from England a series of cases involving anal lesions.[1] More relevant to our immediate experience, Dr. Elias Jacobs has reported a large number of cases observed in San Francisco.[32] Typically rectal herpes presents with pruritus and then intense pain, which may radiate to the groin, the buttocks and the upper thighs. The extreme level of pain may reflect direct assault on nerves by the virus. The patient may become constipated because of pain upon defecation and may have a rectal or anal serous discharge. On examination, one may see lesions on the anus or spreading onto the natal cleft. If seen early, there will be a clear vesicle with an erythematous base. Later an aphthous ulcer appears, looking similar to an oral canker sore, and associated with bilateral inguinal lymphadenopathy. The diagnosis is confirmed by inclusion bodies in cells smeared from the lesion, by viral culture or by acute and convalescent serology for herpes. There is always a problem differentiating between an herpetic ulcer and a syphilitic ulcer, and VDRL determinations must be followed in all such cases.

The clinical course may vary, but presentation is most severe on the initial episode and the recurrences are usually milder. The duration is given as approximately 11 days in both published series.[1,32] Treatment with steroids is contraindicated because of the possibility of disseminating

the process. Sitz baths may help, but if maceration occurs they must be discontinued. If one can make the diagnosis, at least the patient can be assured that the lesions will be self-limited. Phototherapy with a light bulb or exposure to the sun is obviously more difficult to maintain than with lip or gingival lesions and has not been particularly successful.

Anorectal Trauma

In addition to the infections from orogenital, oroanal or proctogenital sexual contact, trauma to the rectum or oropharynx may occur. Kazal and Sohn report a high incidence of hemorrhoids, nonspecific proctitis, anal fissures and fistulae in a homosexual population engaging in anal intercourse.[3,4] However, their findings may be skewed by self-selection since all these patients presented to a proctology clinic. The survey of gynecologic patients by Bolling is probably more representative of the range of trauma from anal intercourse alone.[5] In these women who presented for other than rectal complaints, Bolling found no evidence of sphincter damage or dysfunction. In addition, sphincter relaxation after insertion of the examining finger, which had been reported as a sign of prior anal intercourse, did not correlate at all with sexual histories. Instead, he found that reflex relaxation in the anal sphincter after insertion of the finger was associated with the degree of relaxation and confidence of the patient. The lack of trauma reported by Bolling may reflect greater consideration shown by persons in continuing relationships manifested by gradual dilatation of the smooth muscle sphincter, gentleness and lubrication. I might indicate that all three are equally important in proctoscopy.

Lubricants may also cause problems. Part of the proctitis reported in rectal gonorrhea may reflect the use of soaps, shampoos and other mucosal irritants which may have been used as available lubricants. Such contact proctitis is recognized by a sharp delimitation shortly above the anus.

Foreign Objects in the Rectum

A related problem is the insertion of foreign objects into the rectum. In manual stimulation of the anus, a patient or a partner may insert a variety of objects. Surprisingly with no anesthesia other than alcohol or street drugs, the hand and indeed the forearm up to the elbow may be inserted into the rectum, which one may bear in mind when patients complain about the insertion of one finger. Occasionally such patients will present with rectal laceration. More commonly we see patients with foreign objects which they are unable to retrieve from the rectum.[33] The range of these objects is exceeded only by the imaginative explanation of how they got there. Objects such as vibrators are presumably inserted for autoeroticism, but conceivably other objects may be inserted to relieve pruritus, to reduce prolapsed hemorrhoids or by accident.

In Boston when I was a student, a disheveled patient presented with a mustard bottle in his anus; he said that he was moving his bowels at the city dump, stumbled and fell backwards on the bottle. If so, he was lucky it did not break. A patient presented at the San Francisco Veterans Administration Medical Center with a number 8 billiard ball impacted in his rectum, and he sagely offered no explanation. Our problem is to remove such objects; it is the problem of the patient how they get there. A variety of procedures have been reported for removal of such objects.[33] The presence of the object is evidence of the distensibility of the sphincter, but anxiety or sphincter spasm in a sober patient may complicate the removal. Topical anesthesia may be sufficient to provide relaxation so that one can extract the object. During sigmoidoscopy, some objects can be grasped with biopsy forceps, drawn to the scope and removed with the scope. Bottles, however, may form suction when the mouth is upwards. One way to combat this is to pass Foley catheters past the object to allow the passage of air and relieve the suction. One may then pull down on the catheters after inflation and pull the object down with them; if nothing else, get the catheters back.

Obstetrical forceps or spoons may be of assistance but usually require caudal anesthesia before they are effective because the patients have often tried heroically to remove the objects before they present to a physician and may have lacerations, fissures, and some additional pain and spasm. It has been suggested in the past that a physician could introduce plaster of paris into bottles when the openings are caudal, and allow it to solidify around forceps before withdrawing the object. Unfortunately the heat of reaction of the plaster of paris may break the glass, and it is a time-consuming procedure. In many instances with large objects, it is probably better to refer the patient to surgery for removal of the objects

under anesthesia through the dilated anus. Laparotomy is rarely indicated.

The severest rectal trauma may be iatrogenic. In treating rectal carcinoma or intractable inflammatory bowel disease, amebiasis or rectal syphilis, which may have a similar appearance, must be excluded before resection. An ileostomy or colostomy may have a pronounced effect on the sexual life of patients who will need much reassurance. Many will, however, be able to function adequately sexually following such operations.[34]

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Important Advances in Clinical Medicine

Epitomes of Progress—Preventive Medicine and Public Health

The Scientific Board of the California Medical Association presents the following inventory of items of progress in preventive medicine and public health. Each items, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in preventive medicine and public health which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Preventive Medicine and Public Health of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Vinyl Chloride-Related Cancer

VINYL CHLORIDE MONOMER is a widely used chemical. It is the parent compound of polyvinyl chloride (PVC), a plastic resin used in innumerable consumer and industrial products, including containers, wrapping film, electric insulation, pipelines, credit cards and many other items. Notwithstanding its many valuable properties, overwhelming scientific evidence now shows vinyl chloride to be carcinogenic to humans. Moreover, medical evidence suggests a strong association between exposure to vinyl chloride and the occurrence of a number of toxic, nonmalignant illnesses involving skin, bones, liver, lungs and blood. Polyvinyl chloride (PVC) and other vinyl chloride polymers are not, at the time of this writing, considered to represent a carcinogenic risk to man.

First produced commercially in the United States in 1927, vinyl chloride gas was for many years regarded by toxicologists as having only moderate liver toxicity. It was once considered for use as a general anesthetic, but its use for this purpose was abandoned in the early 1930's after experiments in animals showed that its anesthetic effects were often accompanied by cardiac irregularities.

Major nonmalignant effects clearly associated with occupational exposure to the gas include acute intoxication; disturbances of liver function; acroosteolysis, often with Raynaud phenomenon and scleroderma, and alterations in pulmonary function, with or without abnormal findings on x-ray studies of the chest. Other effects, such as alterations in the cellular elements of the blood, have been reported by some authors in persons who work with vinyl chloride, but confirmation by other authors has not been uniform.

There is some evidence that in workers exposed to vinyl chloride there may be an increased frequency of chromosomal aberrations. It has been alleged that in wives of men who work with vinyl choride there may be a greater than usual fetal death rate and that mothers living in communities near PVC production facilities may be at an increased risk of giving birth to children with birth defects. It must be emphasized that, at the time of this writing, a causal relationship between vinyl chloride exposure and these latter phenomena—excess fetal death rate and birth defects—is not only unproven but is the subject of serious scientific dispute.

In January 1974 Creech and Johnson reported three cases of angiosarcoma of the liver in workers employed in a polyvinyl chloride polymerization plant in Louisville, Kentucky. Angiosarcoma

is a malignant tumor composed of neoplastic endothelial cells. It is also known by the synonyms hemangiosarcoma and malignant hemangioendothelioma. The tumor may originate in organs other than the liver, although at the time of this writing, all reported vinyl-chloride-associated angiosarcomas appear to have originated in the liver. This type of tumor has been considered to be extremely rare, appearing at a rate of only 0.05 to 0.2 new cases per million population (25 to 30 new cases reported in the United States each year). Consequently, it became immediately apparent that the Louisville cluster of cases was unlikely to be due to chance and further studies were undertaken by Creech and Johnson as well as other investigators. As a result of these studies, which included studies in other groups of people working with vinyl chloride as well as experimental exposure to laboratory animals, vinyl chloride was strongly implicated as an agent capable of causing angiosarcoma of the liver in both humans and experimental animals. By December 1975 a total of 45 cases of angiosarcoma of the liver had been discovered throughout the world, and many more have been reported since then. In practically all of them there has been documented occupational exposure to vinyl chloride.

In addition to angiosarcoma of the liver, exposure to vinyl chloride has been found to be associated with an excess of other types of cancer. An excess of liver and biliary cancer was shown in one study, although similar epidemiologic studies of workers exposed to vinyl chloride have not verified these findings. There have been isolated case reports of liver cancer occurring in persons with possible environmental exposure, such as neighborhood or household exposure, but because liver cancer is not so rare as angiosarcoma of the liver, these findings are only suggestive. A number of studies have found an excess of central nervous system tumors in workers exposed to vinyl chloride, when compared to United States population figures. The type of central nervous system tumor most often associated with vinyl chloride exposure is glioblastoma multiforme. Several epidemiologic studies have found an increased risk of cancer of the lung in those who work with vinyl chloride. However, since other studies have failed to confirm this finding, a causal association between vinyl chloride and lung cancer must, at this time, remain suggestive rather than conclusive. Several studies have shown an excess of cancer of the lymphatic and hematopoietic systems in workers exposed to vinyl chloride. One major study suggested that the increased risk is for lymphoma rather than for leukemia. In summary, it may be said that angiosarcoma of the liver remains the type of cancer most clearly identified with exposure to vinyl chloride. However, cancer of other sites may eventually be added to the list of accepted vinyl chloride-related malignant conditions.

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Essential Hypertension, 1979—Where Do We Go From Here?

THE POSITIVE ASSOCIATION between the level of blood pressure (both systolic and diastolic) and mortality is no longer in dispute. Nor is there any argument about the efficacy of antihypertensive treatment. What needs emphasis is the fact that the rate of mortality associated with hypertension is numerically related to the level of blood pressure, even in the range not considered extreme (for example, diastolic blood pressure of 85 to 90 mm of mercury).

Control of hypertension poses two problems for practicing physicians. The first is attitudinal. Patients must be convinced of the necessity for a lifelong commitment to treatment, and thereby be motivated to comply with the prescribed regimen. One of the most important reasons for failure to control hypertension is noncompliance by patients. Ironically, the underlying cause of noncompliance is, in most cases, attitudinal and not drug-induced side effects.

The second problem is the sheer magnitude of the hypertension problem. Prevalence of hypertension in the United States is 18 percent in whites and 38 percent in blacks. About 42 percent of excess deaths attributable to hypertension occur among persons with diastolic blood pressure in the range of 90 to 100 mm of mercury who are by and large asymptomatic and may not even seek medical care. This makes hypertension a public health problem in addition to being a problem in the daily practice of medicine.

Control of hypertension in the community must be based on a creative partnership among all members of health professions so that a serious program of control can be organized for the benefit of the community as a whole. Such a pro-

gram goes beyond merely treating the sick who may or may not seek medical care. Rather, it includes the enlistment of a cadre of different professional disciplines to work together with one common objective: to control hypertension.

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Hepatitis, Immune Globulins and Vaccines

IMMUNE SERUM GLOBULINS (ISG) are sterile solutions containing antibodies derived from human blood. Protection against hepatitis A is conferred by ISG administration within one to two weeks after exposure to hepatitis A as well as preexposure prophylaxis.

ISG manufactured after 1972 has detectable antibody to hepatitis B (anti-HB_s) present in low titer. In addition, hepatitis B immune globulin (HBIG) of high anti-HB_s titer (usually 1:100,000) is available. Both preparations offer some protection before exposure and soon after exposure to hepatitis B. The following suggestions may aid you in selecting prophylaxis for hepatitis B.

Preexposure Prophylaxis

Institutions with high-risk areas, such as hemodialysis units, or custodial institutions for mentally retarded persons should consider routine serologic screening of their employees for anti-HB_s. This will avoid costly and unnecessary use of immune globulins after acute exposure in a person with antibody. At present it appears impractical to recommend use of HBIG in persons with continued exposure to HB_s antigen. Current costs to pharmacies of HBIG is 75 to 100 times per ml the cost of ISG. For large numbers of persons, where globulin use is desired, ISG should be considered for immunoprophylaxis.

Postexposure Prophylaxis

The presence of HB_s antigen appears to correlate well with infectivity and when a test for this becomes commercially available will provide a useful tool in assessing the risk of acute exposures.

HBIG is most useful following a single acute exposure to a relatively large inoculum of HB virus, such as accidental needle stick, mucosal exposure, blood spill on an open wound. HBIG, 0.05 to 0.07 ml per kg of body weight, should be administered as soon as possible and the dose repeated in 25 to 30 days.

Infants born to mothers with acute B hepatitis in the third trimester, or mothers in whom tests are positive for HB$_s$ antigen, should be given HBIG, 0.13 ml per kg of body weight, or ISG, 0.5 ml per kg of body weight in a single dose.

Immune globulin should be administered as soon as possible after acute exposure or birth. It is preferable to give ISG at once, rather than delay prophylaxis more than two days while obtaining HBIG. Administration of two doses approximately one month apart appears to be superior to one larger dose given early.

The use of immune globulin in cases of sexual contact or acute hepatitis B is an unsettled area. HBIG does offer protection to sexual contacts even when administered weeks after exposure, but this may reflect the reduced amount of virus present in saliva and genital secretions as compared with blood. For the present, ISG or HBIG would seem of benefit in a sex partner who does not have HB_s antigen or anti-HB_s.

Experimental hepatitis B virus vaccines show promise in initial human and animal trials. In animal trials the vaccine has been useful when administered after exposure to virus (because of the long incubation period), as well as before virus exposure. In initial human trials, the vaccine appears to be safe, to induce antibody in most employees and patients, and to provide protection against hepatitis B. Use of hepatitis vaccine in high-risk groups may be reasonable in the near future.

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Rabies Treatment Update

HUMAN DIPLOID CELL strain rabies vaccine is now available through the Center for Disease Control on a limited, experimental basis. Patients may be eligible for the vaccine if they have been bitten by a *proven* rabid animal, have a serious allergy to duck embryo vaccine or in whom there is no response to therapy with duck embryo vaccine as shown by an adequate antibody titer rise. Human diploid cell strain rabies vaccine stimu-

lates a much higher antibody response than duck embryo vaccine and at least at this point has *not* been associated with any serious anaphylactic, neuroparalytic or systemic reactions.

Physicians are again reminded that bites from gophers, squirrels, rats, mice, hamsters, rabbits, chipmunks, muskrats, guinea pigs, moles and chinchillas seldom if ever require systemic antirabies treatment. On the other hand bites from animals such as bats, bobcats, coyotes, foxes, skunks and other feral species should be considered as rabies exposure until proven otherwise.

DONALD G. RAMRAS, MD

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Malaria Prophylaxis

ON MARCH 10, 1978 the Parasitic Disease Division of the Center for Disease Control (CDC) published a supplement entitled *Chemoprophylaxis of Malaria* which includes recommendations to travelers and a comprehensive review of the agents available. The following is a brief summary:

Chloroquine phosphate is the drug of choice for suppression, that is, prevention of clinical symptoms of malaria by strains sensitive to the drug. The recommended adult dose is 500 mg (300 mg base) taken weekly; 5 mg per kg of body weight base for children taken weekly beginning two weeks before entering a malarious area and continuing for six weeks after leaving. In this dosage, side effects other than gastrointestinal disturbances—headache, dizziness and blurred vision—are rare. These adverse reactions may be reduced by taking chloroquine with meals. Travelers should be told that this regimen may not protect against chloroquine resistant forms.

Chloroquine suppresses the erythrocytic stages of Plasmodium and if the above regimen is followed, Plasmodium falciparum and Plasmodium malariae, which do not persist in exoerythrocytic phases, will usually be eradicated.

Infection with Plasmodium vivax and Plasmodium ovale may persist in the liver and produce delayed attacks. The exoerythrocytic form is eliminated by a two-week course of primaquine, 15 mg daily for adults and 0.3 mg per kg of body weight daily for children. The use of primaquine for prophylaxis should be reserved for travelers heavily exposed to malaria, who do not have glucose-6-phosphate dehydrogenase (G6PD) deficiency. This drug is not recommended for pregnant women.

Cases of chloroquine-resistant P. falciparum have been documented in Panama, South America, India, Southeast Asia, New Guinea and, most recently, in persons returning from Africa. Travelers may consult their health department or the CDC for information about specific countries. A combination of pyrimethamine and sulfadoxine is an effective suppressive agent for chloroquine-resistant P. falciparum. It is not at present available in the United States but may be purchased in other countries. Travelers may start taking chloroquine before entering the malarious area and then take pyrimethamine, 50 mg, and sulfadoxine, 1,000 mg, once every two weeks continuing for six weeks after last exposure in a malarious area. This combination is active against the erythrocytic stages of malaria. Pyrimethamine-resistant strains of P. vivax will not be suppressed. This preparation is not recommended for pregnant women.

As with all medications, travelers are advised to take a sufficient supply with them for the entire trip. Clinicians should remember that the incubation period of malaria may be prolonged for months in persons who have taken antimalarials. Serologies (done by the Center for Disease Control) are useful in cases in which there is a question of mixed infection where primaquine therapy is being considered.

MICHELE MICHAELS GINSBERG, MD

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Joy of the Communal Bath or Don't Go Near the Water

AS HOT TUBS, whirlpool baths and pools become a more regular feature of private and public recreation, clinicians can expect to see the infectious complications of these communal pools. Common offending agents include Pseudomonas aeroginosa, Staphylococcus aureus, viruses including enteroviruses and adenoviruses, and Mycobacterium marinum.

Several outbreaks traced to Pseudomonas aeroginosa serogroup 11 contamination of whirlpools have been recognized. High temperatures and

activation of water makes maintainence of proper disinfectant residuals (0.4 ppm of free chlorine) difficult in whirlpools. Eradication of Pseudomonas, an organism adapted to water and capable of growth at 42°C, is a special problem. High water temperature and hydration may alter the skin; that is, dilate pores and promote infection with Pseudomonas. Skin manifestations of Pseudomonas infection include pruritic papulovesicular or vesiculopustural rash which develops 8 to 48 hours after exposure, and usually resolves over a period of seven to ten days without specific treatment. In addition, sore throat, sore eyes, fever, malaise, nausea, vomiting and otitis externa have occurred following exposure to Pseudomonas infected water.

Swimmer's ear or diffuse otitis externa may be caused by Pseudomonas, Staphylococcus, Escherichia coli and Enterobacter aerogenes. Therapy usually consists of administering local otic preparations containing antibiotics, such as colistin or neomycin. Recurrent swimmer's ear may be treated prophylactically with a solution such as 2 percent acetic acid in glycerin base instilled in the canal after swimming.

Epidemic adenovirus conjunctivitis and pharyngo-conjunctival fever have resulted from swimming pool contamination. Most outbreaks have been related to inadequate chlorination. The incubation period is five to nine days, and fever, pharyngitis and conjunctivitis are characteristic. Adenovirus infection is usually self-limited.

Mycobacterium marinum is the etiologic agent of swimming pool granuloma or chronic granuloma of the skin. The skin lesion usually results from trauma to the skin (often forgotten) in a swimming pool or while cleaning a fish tank. A small, red, nontender papule that may drain pus intermittently results. The lesions may resolve spontaneously or may require chemotherapy, such as with minocycline hydrochloride, or surgical excision.

If you suspect that a patient has acquired disease from a communal pool, contact your local health department so that an epidemiologic investigation and sanitation inspection can be undertaken.

MICHELE MICHAELS GINSBERG, MD

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Screening Methods for Tuberculosis Control

THE COURT PHYSICIAN in China approximately 2,000 years ago is reputed to have advised the emperor that "to administer medicines to diseases which have already developed . . . is comparable to the behavior of those persons who begin to dig a well after they have become thirsty, and of those who begin to cast weapons after they have engaged in battle." Would not these actions be too late?

Similarly, the Center for Disease Control in recent years has changed the thinking in regards to the status of tuberculosis control. First, they state that 80 percent of future active cases will come from the pool of persons who were infected with mycobacterium tuberculosis years ago and in whom the bacilli remain dormant. The other 20 percent will be contacts of recently identified infectious cases. Before 1976 most cases nationwide were found in persons 45 years old and older. The incidence of tuberculosis among older persons continued to increase nationally, but in California more new cases are seen now in persons younger than 45.

Program objectives in any tuberculosis control program are as follows: (1) infectious persons must become noninfectious, (2) noninfectious persons (who are infected with tubercle bacilli) must remain noninfectious and (3) persons not infected must remain not infected. In order to achieve these objectives, the classification of tuberculosis was changed in 1974. The following is the currently accepted classification:

0. No tuberculosis exposure, not infected (no history of exposure, negative tuberculin skin test).

I. Tuberculosis exposure, no evidence of infection (history of exposure, negative tuberculin skin test).

II. Tuberculous infection, without disease (positive tuberculin skin test, negative bacteriological studies [if done], no x-ray findings compatible with tuberculosis, no symptoms due to tuberculosis).

III. Tuberculosis: infected, with disease.

Classifications I and II are where the current emphasis of control programs is now directed. The intimate contacts of a classification I patient, especially infants and children, are advised to be placed for a minimum of three months on an appropriate isoniazid course of chemotherapy

after contact with the case is broken. If they are still a classification I at that time, therapy may be discontinued. It is recommended that all classification II patients 35 years of age and under be given an appropriate course of isoniazid chemotherapy.

Screening for tuberculosis today is best accomplished by use of the Mantoux intradermal tuberculin skin test (5 TU of purified protein derivative S in Tween 80 media). A test result read 48 to 72 hours later of 10 mm or greater induration is judged to be positive. In close household contacts to an index case, greater than 5 mm induration may be considered positive for starting isoniazid chemotherapy. A history of BCG (bacille Calmette Guérin) immunization may confuse the interpretation of the skin test results. However, standard procedure is to consider a purified protein derivative reaction of 10 mm or more as indicative of true infection. All cases in which a skin test is positive should be followed up with x-ray evaluation of the patients' chest status.

A person considered to be a tuberculin converter is one in whom there has been a positive skin test of less than 10 mm induration within the last two years, in whom on retesting there was an increased induration of 6 mm or greater, and in whom a test result now is 10 mm or greater in induration. In such persons an appropriate course of chemotherapy is advised.

Tuberculosis control must continue to be a priority in certain areas of the country. Geographically, the distribution of cases is uneven. In California, the tuberculosis case rate continues to be higher than the national rate (15.8 per 100,000 population compared with 13.9 per 100,000 population). A total of 3,465 new active cases were reported in California in 1977 (compared with 30,145 cases nationally). These cases were concentrated in the large metropolitan areas of the state and agricultural regions of the Central Valley. Data on ethnic distribution of cases support the observation that the increase in cases is due largely to the influx of immigrants from Latin America, Asia and Oceania. Children nationally account for 5.5 percent of reported cases, compared with 8.5 percent in California.

Tuberculosis continues to be a costly major public health problem. Therefore, alertness to the disease by private practitioners, early diagnosis, timely initiation of therapy, prompt reporting and effective follow-up of contacts continues to warrant increased attention and effort.

STEPHAN BILLSTEIN, MD

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EDITORIALS

Sears Suit

THE CLASS ACTION SUIT recently filed by Sears Roebuck and Company against ten federal agencies scratches at the tip of what must be a huge iceberg. The scratch touches only upon the composition of the work force of one company, and the absolute impossibility of its compliance with the pertinent government laws and regulations. The iceberg consists of the plethora of laws, rules and regulations which sometimes seem almost to make a mockery of the law itself and which seem gradually to be stifling the progress and change that is so necessary if this nation is to have a position of leadership in the modern world. This iceberg has become very large, it is growing, and it already sits very deep in the national water.

In our system of government there are legislative, judicial and executive branches, each functioning at local, state and national levels. Thus there are nine major loci of power and control. The legislative branches busily pass laws, the judicial branches make case law at a more leisurely pace, and the agencies of the executive branches crank out hundreds of regulations which have the force of law. There is no real coordination of all these mechanisms. Conflicts and inconsistencies are bound to occur and the legal recourse to resolve them is cumbersome, time-consuming and inefficient at best. It may take years to resolve the Sears suit, and much, much longer to correct the serious disorder that gave rise to it.

All of this suggests that our system of laws and regulations may somehow be intrinsically ill-adapted to govern today's complex, interdependent, ever-changing social and technologic system as it is developing in this nation. As American society becomes more complex and interdependent (and it is doing this very rapidly) the need to assure some order in this system becomes more pressing. So far the response has been for government to pile law upon law and regulation upon regulation. But somehow this has not produced the desired order. Instead of oiling the machinery to make it run more smoothly and efficiently, too often the opposite has occurred. Friction has been introduced, additional and unnecessary costs have been incurred without commensurate benefit, and progress and needed change have become ever more difficult to accomplish. While the world is moving on we seem to be legislating and regulating ourselves into relative stagnation and immobility with our multiplying, conflicting and often unworkable laws and regulations.

The solution will not be easy to find. Our regulatory efforts seem to be producing more disorder than order. If we are to maintain, or some might say regain, our position of leadership toward a better world (which we believe to be our national heritage and destiny), then it would seem that we must find ways to escape what is fast becoming legislative and regulatory chaos, and to release ourselves from those unnecessary and self-imposed legislative and regulatory bonds that are sapping our strength and to some extent even our will.

Sears Roebuck and Company is to be commended for applying a little heat to this iceberg and it is to be hoped that in time, and perhaps with more heat, the iceberg itself can be reduced to more manageable size. The health care enterprise has much at stake in all of this.

—MSMW

Does Hypophysectomy Have a Role in the Current Management of Breast Cancer?

THERAPEUTIC APPROACHES to carcinoma of the breast throughout its frequently complex course comprise a broad array of procedures and protocols for treating both the primary tumor and the many manifestations of metastatic disease. Within the last decade, cytotoxic chemotherapy has been applied as an adjuvant to primary treatment, and its success in this role is a matter of record. Concurrently, chemotherapy has been used with ever-increasing enthusiasm and effectiveness in the management of the disseminated disease. Because chemotherapy at present occupies center stage, and quite correctly so, physicians are inclined to forget the proven efficacy of irradiation and hormone therapy, including endocrine ablation, as therapeutic modalities for advanced breast cancer.

In this issue, the article by Silverberg and Britt

constitutes a forceful argument for the effectiveness of transsphenoidal hypophysectomy as a palliative measure in treating carcinoma of the breast and prostate. In previous years, when craniotomy was the preferred method of hypophysectomy, adrenalectomy was considered a less hazardous therapeutic approach to these types of cancer. Although pituitary ablation was known to produce slightly, but significantly, superior therapeutic results, adrenalectomy was regarded as a satisfactory alternative—possibly because the roles of growth hormone and prolactin in the evolution of these disorders was still poorly understood. With the advent of current stereotactic and transnasal procedures for pituitary ablation, the advantages and superiority of hypophysectomy in the treatment of breast and prostate cancer cannot be questioned.

The recognition of estrogen receptors in breast cancer cells has provided an alternative to the therapeutic trial as a means of anticipating a tumor's hormone-dependence. The correlation between the presence of estrogen receptors in a tumor and the extent to which that tumor is hormone-responsive is less than perfect—but, as reflected in Silverberg's small series, most patients bearing estrogen receptor-positive tumors respond to hypophysectomy, and few whose tumors are receptor-negative derive benefit from the procedure. Recent evidence strongly suggests that patients with receptor-negative tumors respond well to cytotoxic chemotherapy, whereas those with receptor-positive tumors have a distinctly inferior response.

To review the many different manifestations of metastatic breast cancer and the preferred methods of management would exceed both my knowledge and the intent of this editorial. The point is this: when palliation of advanced disease is the problem at hand, select the form of therapy that is judged to be most appropriate because of the predicted outcome and the possible morbidity. For example, it would be inappropriate to treat a solitary, painful metastasis to the femur by chemotherapy or hypophysectomy, rather than by local irradiation. In treating a patient whose disease is widely disseminated and dominated by multiple osseous lesions, the initial approach could be selected on the basis of information from an assay for estrogen receptors in tumor taken at the primary operation or removed from an accessible metastasis. In cases of receptor-positive tumors, oophorectomy would be the first maneuver for managing premenopausal patients, and hormonal therapy for postmenopausal patients, with hypophysectomy as a secondary treatment for responders at the time of relapse. For receptor-negative patients, present experience argues for cytotoxic chemotherapy at the outset. If the estrogen-receptor activity of the tumor has not been determined, and if removal of a metastasis (for example, to a superficial lymph node) is not a reasonable course to follow, then local practice will determine the first approach to management. Here I take the editorial liberty of expressing my prejudice for pursuing hormone therapy initially, for *if* the tumor is sensitive, an objective remission that may last for many months, or even a few years, is a realistic expectation.

Hormone therapy and ablation of endocrine organs are intended only for palliation of the disease. One day in the future, cytotoxic chemotherapy—possibly in concert with immunologic enhancement—will cure disseminated cancer of the breast. When that day arrives, palliative forms of therapy will be relegated to the annals of medical history. Nevertheless, the cure of advanced disease is still in the dim future; in the meantime, hypophysectomy can and should be used to its best advantage. For many patients who cannot be cured, the judicious and sequential application of available therapeutic approaches can convert breast cancer to a chronic disease.

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Stroke Prevention

THOUGH THE ECONOMIC COST and mortality due to strokes are staggering, they still are secondary to the social trauma experienced by disabled stroke victims. The total value of stroke prevention is nearly impossible to evaluate. An aging population portends a socioeconomic problem of ever increasing magnitude.

Dr. Herbert Machleder's Medical Progress article in this issue clearly expresses the importance of early and accurate detection and evaluation of transient ischemic attack (TIA) and asymptomatic bruits. The problem of stroke is well presented in the paper and we welcome a sound, rational approach to the detection and prevention of potential strokes in stroke-prone persons. Pinpointing the stroke problem to those with increased risk factors may be ideal, but one cannot

ignore the consequence of strokes in lower risk groups as well. Therefore, universal awareness and detection of stroke-prone persons must be achieved.

Further amplification perhaps is warranted in certain aspects of this excellent article. With the exception of the very thin neck and the low carotid bifurcation, it is doubtful that many physicians will find cervical carotid pulse palpation reliable for carotid evaluation. Although auscultation for cervical carotid bruits is extremely important in physical examinations, attempting to define their significance by auscultation is fraught with error. The soft bruit of insignificant stenosis may be indistiguishable from the barely audible bruit of 80 percent to 90 percent stenosis. Also, the vagaries of memory make sequential evaluation by auscultation difficult at best. Hard copy recordings such as those obtained by carotid phonoangiography assist in evaluating the significance and progression of cervical bruits. We have also noted that cervical bruits with well defined diastolic component are essentially diagnostic of a tight internal carotid stenosis.

The emphasis on noninvasive evaluation in the detection of prestroke lesions is well justified. It should be pointed out, however, that—contrary to the author's statement—other noninvasive testing modalities have achieved equally widespread application with excellent diagnostic accuracy.[1-3] In contrast to pressure measurements by oculopneumoplethysmography, oculoplethysmography, a flow related test, and carotid phonoangiography, an audiovisual analysis of carotid bruits, have been used in many clinical laboratories for several years with excellent reliability. Newer ultrasonic imaging techniques which may in part eventually supplant arteriography show considerable potential. It can be anticipated that future developments and refinements will further enhance the noninvasive evaluation of carotid lesions.

The discussion emphasizing the lack of direct correlation between symptoms and localization of the arterial lesion is very appropriate. Many patients presenting with "nonhemispheric TIA's" of apparent vertebro-basilar origin may be relieved by endarterectomy of severe carotid stenosis. We have found there to be no significant difference in stroke incidence between patients with asymptomatic bruits and those patients with bruits and nonhemispheric symptoms.[4] Our experience shows a 20-percent stroke rate in such patients with greater than 70-percent stenosis over an average of 24 months of follow-up. On this basis prophylactic surgical therapy is recommended for asymptomatic patients with greater than 70-percent stenosis. Lesser degrees of stenosis are followed noninvasively at appropriate intervals or until the onset of TIA's, thereby avoiding unnecessary arteriography with its attendant risks and expense. The interval between studies is determined individually depending upon the character of the bruit and rate of progression since some lesions have been observed to progress rapidly in three to six months.[5] Potential ulcerative lesions are not considered for arteriography and surgical operation until the onset of TIA's or the progression to greater than 70-percent stenosis by noninvasive evaluation.

The limitations of medical therapy are documented by the current studies utilizing platelet antiaggregate therapy. This approach has shown promise but the select subgroup deriving benefits severely limits its potential application. For an average of 24 months we have followed the cases of 832 patients with cervical bruits but without lateralized symptoms or significant stenosis by oculoplethysmography. The incidence of carotid stroke without specific medical therapy was 0.7 percent.[4] This suggests that absence of significant internal carotid stenosis is a greater factor in a low incidence of stroke than is utilization of a specific medical therapy.

Dr. Machleder's article provides a comprehensive analysis of the socioeconomic problem of strokes, the importance and feasibility of detecting stroke-prone persons, and a sound rationale for the roles of medical therapy and surgical operation in stroke prevention. However, the emotional and economic impact of stroke should not provide an open license for carotid operations, the use of which should be limited to those physicians with adequate training and expertise to achieve acceptable morbidity and mortality.

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CASE REPORTS

Refer to: Lowe J, Hecton A: Wegener granulomatosis with avascular necrosis of a lower extremity. West J Med 130: 256-259, Mar 1979

Wegener Granulomatosis With Avascular Necrosis of a Lower Extremity

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WEGENER* GRANULOMATOSIS with its common presentation of the generalized form involving upper and lower airways, as well as the kidneys, is diagnosed by its histologic hallmark of necrotizing granulomatous vasculitis. This has been a uniformly lethal disease since the first three cases reported by Wegener in 1936[1,2] until the early 1960's when maximal survival time was approximately five months. During the 1960's beneficial effects of corticosteroid therapy as well as therapy with various cytotoxic agents, either used alone or in combination with corticosteroids, were reported in the literature.

More recently, significant therapeutic responses have been reported in two studies of long-term follow-up of patients treated with cyclophosphamide.[3,4]

The following is a case report of Wegener granulomatosis with an unusual complication as illustrated by accompanying illustrations.

Report of a Case

A 62-year-old white man was admitted to the hospital in October 1975 because of a sudden loss of vision in his left eye. He was well until two months previously when symptoms of an upper respiratory infection developed. A few weeks later, he presented with maxillary sinusitis which required drainage and appropriate antibiotic therapy (Enterobacter sp) as an inpatient.

From Huntington Memorial Hospital, Pasadena, California.

Submitted, revised, April 10, 1978.

*The WESTERN JOURNAL's style regarding eponyms is that they are not written in the possessive form; therefore, Graves disease, Ewing sarcoma and Paget disease. An explanation may be found on page 78 of the July 1978 issue.

Reprint requests to: Judith Lowe, MD, Huntington Memorial Hospital, 100 Congress Street, Pasadena, CA 91105.

Figure 1.—Spontaneous, draining ulcerations on scalp.

After the patient left the hospital, the vision in his left eye deteriorated rapidly, although an ophthalmological examination showed no abnormalities. X-ray studies of the skull showed a destructive process of the left lesser wing of the sphenoid bone along the superior margin of the superior orbital fissure and the patient was readmitted for further studies.

On physical examination, he appeared alert and oriented but almost completely deaf, having the ability to hear only loud sounds very close to his right ear. Body temperature ranged between 37.2° and 38.3°C (99° and 101°F). Pulse was 130 beats per minute and regular, and respirations 30 per minute. Blood pressure was 120/70 mm of mercury.

There were multiple draining skin lesions on the scalp and left leg (Figure 1), and also tender, purple, subcutaneous nodules in both legs. The left pupil was fixed and nonreactive to light with impairment of ocular movement and lid ptosis. The left tympanic membrane was opaque and yellowish. The nasal mucosa was dry with scanty dried secretions. Pressure over the maxillary and frontal sinuses did not elicit tenderness. The throat was clear, without ulcerations or exudates and the palate was intact. No lymph node enlargement was present.

Mild expiratory wheezes were present on lung auscultation. The heart was normal except for tachycardia. Findings on abdominal examination were normal.

Neurological examination disclosed left third cranial nerve palsy as described above and testing of the eighth cranial nerve showed intact bone conduction and decreased air conduction. Sensation in both feet was diminished in a "stocking

pattern." The peripheral pulses were symmetrical and strong except the dorsalis pedis which were not palpable bilaterally.

The blood count showed a hemoglobin of 10.9 grams per dl with a hematocrit of 44.9 percent. Leukocyte count was 13,800 per cu mm, and the platelets were reported to be normal to slightly increased. Analysis of urine showed 20 to 25 red blood cells per high-power field. The serum alkaline phosphatase value was 240 mU per ml (normal limits 30 to 85 mU per ml). The erythrocyte sedimentation rate (by Westergren method) was 90 mm per hour (it had been 30 mm per hour two weeks earlier).

X-ray studies of the skull showed severe demineralization and osteolytic destruction of the superior wing of the left optic foramen and left lesser wing of sphenoid and also along the superior margin of the superior orbital fissure. Results of a brain scan were normal. A bone scan showed increased uptake in the left facial bones. An x-ray study of the chest showed infiltrates which developed bilaterally in the interval since the last admission. A lung scan showed bilateral multiple defects suggestive of either pulmonary emboli or bronchopneumonia.

Consultation with an ear, nose and throat specialist established that a nasal septum perforation took place in the two week interval since the patient's previous admission. Biopsy specimens were taken from the nasal septum and ethmoid bone as well as from subcutaneous nodules and skin ulcerations. The microscopic lesions of necrotizing vasculitis and granulomata were present in all specimens (Figures 2, 3 and 4).

On the seventh day after admission, tachycardia developed and the patient became increasingly dyspneic. Studies of arterial blood gases showed hypoxia, increase in the alveolar-arterial gradient and uncompensated metabolic acidosis. An electrocardiogram showed arrhythmias: transient bige-

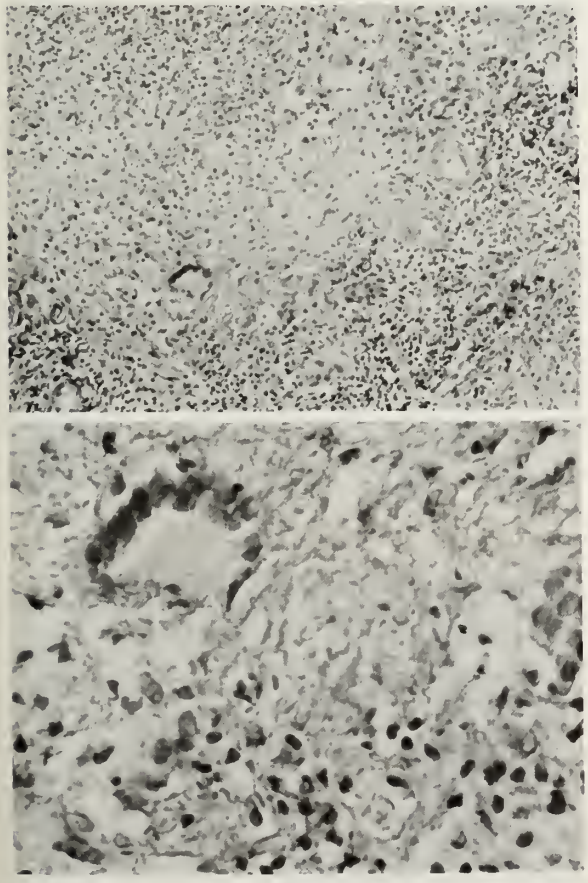

Figure 2.—Top, Necrotizing granuloma in ethmoid bone biopsy (reduced from 100×). **Bottom.** Necrotizing granuloma in ethmoid (reduced from 400×).

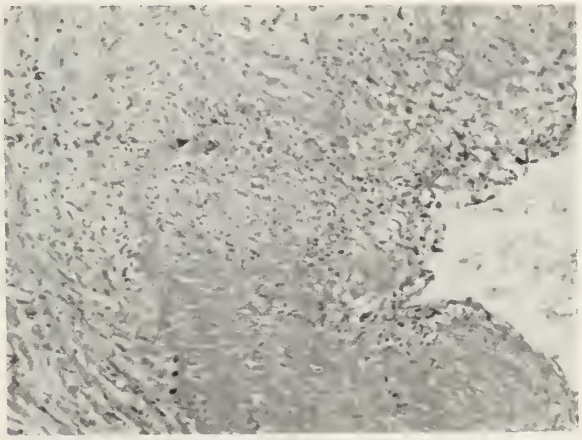

Figure 3.—Inflammatory granulation tissue in subcutaneous lesion of right leg (reduced from 40×).

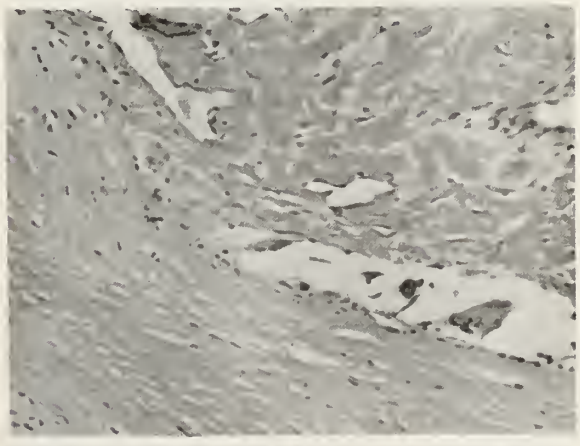

Figure 4.—Necrotizing inflammation with presence of giant cells in subcutaneous blood vessel; organizing thrombosis in this vessel can be seen.

miny, wandering atrial pacemaker and eventually atrial fibrillation with venticular rate of 120 per minute. The patient was transferred to the intensive care unit and his condition monitored. On the eighth day after admission, the clinical suspicion of Wegener granulomatosis was confirmed and the treatment with cyclophosphamide at a dose of 125 mg per day given orally was started. An x-ray film of the chest showed development of bilateral infiltrates and the red blood cells in the urine sediment increased to 150 to 175 per high-power field. The leukocyte count was 14,000 per cu mm, and the platelet count was 715,000 per cu mm. On the tenth day after admission, pain developed suddenly in the patient's left foot with cyanosis and decreased capillary filling. The pulse of the left posterior tibial artery was not palpable. At the same time as the apparent embolic incident, numerous new subcutaneous nodules appeared on the lower left leg. An embolectomy was carried out the next day, but restoration of arterial circulation was not achieved.

In view of the deterioration of the clinical condition as expressed by extension of lung infiltrates, increase of number of red blood cells in the urine sediment and decrease of the creatinine clearance from 114 ml per minute to 70 ml per minute, the cyclophosphamide therapy was continued with a daily dose of 200 mg given intravenously.

On the 18th day, the left leg was amputated below the knee. Pathological examination gave the following findings: (1) Occlusive arteriosclerosis of peripheral vessels with organizing thrombus of the left anterior tibial artery, (2) granulomatous vasculitis with necrosis in adjacent muscle tissue (Figures 3 and 4) and (3) ulcer of leg (Figure 5).

The postoperative course was satisfactory. After eight days of intravenous administration, cyclophosphamide was continued orally at a daily dose of 125 mg (1.5 mg per kg of body weight).

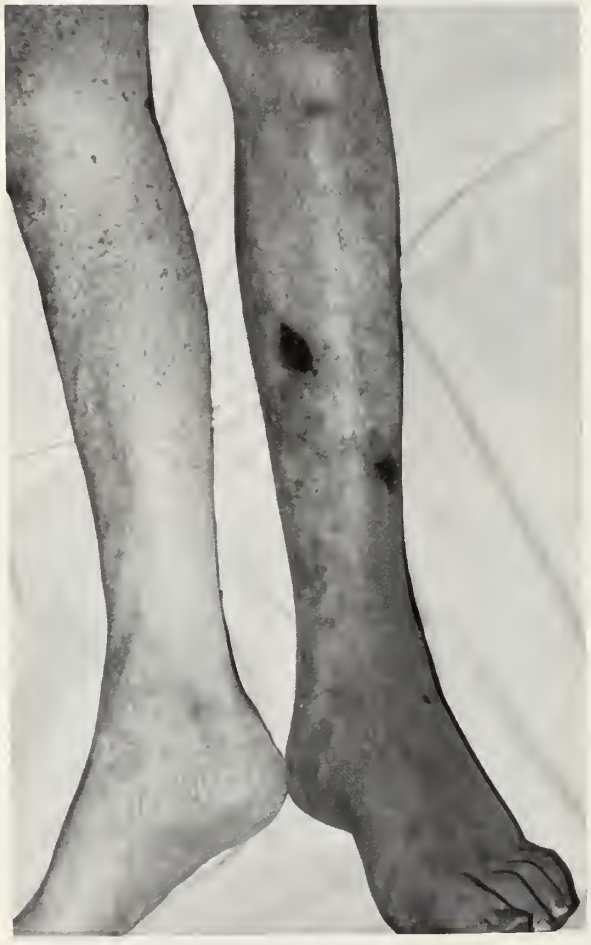

Figure 5.—Subcutaneous nodules, one of them spontaneously ulcerated on leg (impaired circulation reflected by cyanosis).

Figure 6.—Healing scalp ulceration after treatment; "saddle nose" due to septal perforations can be seen.

Figure 7.—Patient shown one year after treatment.

There was pronounced clinical improvement as assessed by the following: (1) clearing of lung infiltrates, (2) spontaneous conversion to sinus rhythm, (3) decrease of number of red blood cells in urine sediment and (4) improvement of creatinine clearance to normal.

The patient was discharged from the hospital after being in the rehabilitation unit, where he received extensive physical and occupational therapy (Figure 6). He has since been in remission and continues to receive 125 mg cytoxan orally per day. The leukocyte count is stable above 3,000 per cu mm, and the platelets eventually returned to the normal range. A prosthetic device for the left leg and use of a hearing aid has made it possible for the patient to resume daily activities. (See Figure 7.)

The arrhythmia that preceded the embolic episode in this case was very likely due to vasculitic involvement of coronary vessels; such occurrences have been reported in the literature.[5] The spontaneous conversion to sinus rhythm along with improvement of respiratory and renal findings on cyclosphosamide therapy seems to confirm this assumption. We also feel that the extensive vasculitic involvement was responsible for the inability to maintain a viable leg due to ineffective collateral circulation.

Summary

A case of generalized Wegener granulomatosis has been presented with typical multisystem involvement including the respiratory tract, kidneys, skin, cranial nerves, heart and hematopoietic system. In addition, a heretofore unreported complication has also been presented, namely avascular necrosis of an extremity, requiring amputation. "Pulseless disease" and avascular necrosis after embolectomy should alert physicians to extensive involvement of collaterals by a vasculitic process.

While the classification and causes of this interesting disorder still remain elusive, the introduction of cyclophosphamide has at least offered a much brighter perspective for improvement and possible cure.[3,4]

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Lithium Poisoning

Report of a Case With Neurologic, Cardiac and Hepatic Sequelae

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LITHIUM CARBONATE is now a well established agent for the treatment of acute mania and for prophylaxis in patients with recurrent manic and depressive bipolar as well as a number of unipolar recurrent episodes.[1,2] The treatment of manic-depressive patients with this agent, its dosage, monitoring schedules, therapeutic blood levels and narrow therapeutic-toxic range have been outlined by Schou[1] and other authors.[3,4]

Lithium toxicity is closely related to serum lithium levels and can occur at doses close to therapeutic levels (see discussion).

Lithium therapy requires extreme caution and thorough knowledge by physicians in situations when patients are on severe diets or have low sodium intake; in cases of heavy fluid loss (diarrhea, vomiting or fever) or cardiac-renal problems; in aging patients with decreased renal clearance, and in schizophrenic and depressive patients, whose tolerance for lithium is lower than that of manic patients.[1,5]

Historically, the use of lithium salts as a substitute for sodium chloride in patients with cardiac disease gave rise to early reports on the neurotoxicity of lithium ions.[6,7]

The clinical manifestations of lithium intoxication have been well documented by Schou.[8] In general, patients have either died or completely recovered, with no lasting neurologic sequelae. Recent evidence indicates, however, that permanent neurologic[9] or cardiac or hepatic damage can result from lithium intoxication. This communication will present such evidence.

Report of a Case

A 36-year-old businessman with a severely obtunded sensorium and with coarse tremors of his extremities was brought into the emergency

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room of a university hospital on January 25, 1975. Ten days before this admission he had been admitted to a private facility for one week and lithium carbonate therapy, 900 mgs three times a day (2,700 mgs) had been started on January 15, 1975 for a depressive illness associated with anxiety. Sulfamethoxazole, 400 mg, and trimethoprim (Septra), an antibiotic, 80 mg, were also prescribed, for prostatitis and recurrent bronchitis.

At the time of discharge, on January 22, 1975, the patient's blood lithium concentration was 1.1 mEq per liter. While at home, January 22 to January 25, he continued on this lithium regimen (2,700 mg per day) and also took six to eight clorazepate (Tranxene) tablets (22.5 mgs per tablet) per day to reduce his pronounced anxiety. He also drank 6 to 12 ounces of alcohol every day.

The patient had anorexia, nausea, some vomiting and diarrhea. As a result of above symptoms, food and fluid intake diminished. On January 24, 1975, he became ataxic, lethargic, and uncommunicative; on the next day he became incontinent of urine and feces.

Past History

The patient suffered from recurrent bronchitis, ulcers, alcoholism, mild hypertension and mood swings (cyclothymic) with anxiety. He had not been treated with lithium before. An electrocardiogram (ECG) and liver function tests in 1974 had shown no abnormalities.

Physical Examination

Positive findings: blood pressure was 140/96 mm of mercury, temperature was 37.2°C (99°F), bilateral exophthalmus was noted. Lungs: there were scattered rhonchi and wheezes. Heart: early midsystolic murmur at left base was noted. Abdomen: right upper quadrant guarding without hepatomegaly was present. Neurologic findings: the patient was semicomatose with roving eyes and frequent blinking; he grunted and sobbed in response to stimulation. Muscle tone was increased, with intermittent coarse tremors. Deep tendon reflexes were equal and hyperactive; there was pronounced bilateral ankle clonus and Hoffman and Babinski signs were present.

Initial Laboratory Studies

On January 25, 1975, the following findings were noted: slight decrease in electrolyte (sodium, chloride, potassium) levels and an increase in levels of uric acid, creatinine, blood urea nitrogen (BUN, 83 mg), leukocyte count, alkaline phosphatase (154 mU per ml), lactic dehydrogenase (LDH, 238 mU per ml), creatine phosphokinase (CPK, 72 mU per ml). Results of glucose, thyroid, brain scan, bilirubin, albumin-globulin ratio, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) studies were normal A roentgenogram of the chest showed left upper lobe infiltrate and atelectasis. An electroencephalogram (EEG) showed diffuse 6 to 7 cps slowing of background frequency and independent 3 to 4, 4 to 5 cps asymmetric slowing in both hemispheres (more prominent in right than left). Serial electrocardiograms (ECG) showed Q waves in leads II, III, AVF; inverted T waves and ST segment depression increasing in amplitude in all precordial leads (V_1-V_5). Later ECG's showed newly inverted T waves in II, III, AVF; QRS axis at −30 degrees. In subsequent laboratory studies (January 26 to January 31), the following changes were seen: SGOT values rose to 235 mU per ml; SGPT to 911 mU per ml, alkaline phosphatase to 178 mU per ml, LDH to 317 mU per ml, CPK to 324 mU per ml; BUN, serum electrolytes, creatinine and x-ray films of the chest returned to normal. Blood lithium levels ranged from an initial 7.6 mEq per liter to 0.9 mEq per liter on the fourth day, 0.7 mEq per liter on the fifth day, 0.5 mEq per liter on the sixth day and 0.1 mEq per liter on the ninth day. Urine lithium concentrations ranged in the first few days from 25 ml per minute to 10 ml per minute.

Hospital Course and Treatment

The patient was given intravenous fluids (dextrose and saline), sodium bicarbonate and potassium chloride. Mannitol was given in 25-gram increments every four hours for three days. Rapid diuresis followed. Other supportive measures, including a respirator, antibiotics and antihypertensives, were also used. Hemodialysis was considered but not undertaken due to adequate response to above treatment.

Progressive improvement in the patient's general physical health and his neurologic status was noted over the next ten days. He had, however, two tonic-clonic seizures, with subsequent transient weakness of the right lower extremity (day three); involuntary grimacing, choreoathetoid movements of the upper extremities, and generalized myoclonic jerks as well as intermittent rage reactions were noted on days seven to nine.

At the time of discharge—at the patient's insistence—18 days after admission, pronounced residual dysarthria, spasticity of lower extremities, ataxia and intention tremor were evident. No organic brain syndrome was apparent.

The patient has been difficult to follow because of his noncooperative, paranoid and hostile behavior. Six months after admission to hospital the neurologic features were only slightly improved. An ECG showed the evolution of an inferior myocardial infarct; results of liver chemistry tests continued to be abnormal.

Discussion

This case raises a number of issues: (1) the possibility of irreversible changes in organ systems hitherto not reported (hepatic, cardiac) due to lithium toxicity; (2) the need for proper diagnosis because response to lithium therapy varies in the different affective syndromes; (3) the use of lithium in patients with affective symptoms, who also abuse alcohol, sedatives or stimulants, or who also take antidepressant and other psychotropic drugs—and the possible complications; (4) use of the drug in patients at special risk, those with fluid and electrolyte imbalance and other medical problems in whom caution with dosage and monitoring is indicated: (5) the need for accurate biochemical indicators to show impending lithium toxicity or clinical improvement; (6) treatment of lithium intoxication.

On the basis of his history, the patient's psychiatric diagnosis would fall into the category of either a schizo-affective illness or an atypical, manic depressive illness complicated by an addiction to alcohol and possibly to tranquilizers. Studies of the typical and atypical affective syndromes with their differing therapeutic and prognostic outcomes have recently been published.[10]

There are, at present, conflicting data on the use of lithium in schizo-affective states,[11-13] in atypical manic depressive patients (mixed affective states) complicated by alcohol and drug abuse,[10,14] and in the acute treatment of depression.[15]

The usual starting dosage of lithium carbonate in *acute mania* is 600 mg three times a day, producing serum lithium levels ranging from 0.5 to 1.5 mEq per liter. When the manic attack breaks (four to ten days), dosage is reduced to maintenance levels of 300 mg three times a day to achieve levels of 0.5 to 1.0 mEq per liter ± 0.25 mEq per liter, since nonmanic patients cannot tolerate the high doses of lithium that manic patients can.

In the treatment of mild hypomanic patients and acutely depressed patients, and in the prophylaxis of bipolar (cyclothymic) patients, the starting doses of lithium are 300 mg twice a day to four times a day to achieve serum levels of 0.5 to 1.0 ± 0.25 mEq per liter. Maintenance doses and blood levels are very close to therapeutic levels and doses.

Lithium toxicity may occur when blood levels start approaching 2.0 mEq per liter. Frequent blood tests to determine lithium levels are advisable during the therapeutic phase of treatment. Lithium toxicity is potentiated in conditions of low sodium or poor fluid intake. Hence normal hydration and salt intake are imperative during lithium therapy.[1-3]

The patient whose case history is presented in this paper had an acute depressive reaction and a history of mood swings. His starting and maintaining doses should have been 300 mg twice a day to four times a day and serum lithium levels in the range of 0.5 to 1.0 ± 0.25 mEq per liter. His serum lithium concentrations should have been monitored more frequently. He should have stayed longer in the hospital to achieve better hydration and food intake, as well as better control over other medication and alcohol intake. Had such a regimen been followed the outcome would most likely have been different.

The neurologic symptoms in lithium intoxication have been thoroughly described by Schou[8] and other authors.[5,9,16] The neurotoxicity of lithium has been known for a long time; lithium-induced confusional states as well as choreoathetotic and parkinsonian syndromes have also been described. However, patients with such syndromes have either recovered fully or have died.[17] Recent evidence indicates that in certain instances irreversible brain damage may result from lithium toxicity.[9] The neurologic structures usually affected are the basal ganglia and cerebellum.

Many studies have recorded ECG changes associated with high doses of lithium.[18] The changes are described as mild and consist of T wave depression, flattening or inversion and a widening of the QRS complex. These are changes similar to those described in potassium balance problems; occasionally, dysrhythmias occurred. In the patient in this report, however, an acute inferior

myocardial infarct developed. This phenomenon has not been reported, to our knowledge, as a complication of lithium intoxication. It is to be noted that the patient had no history of cardiac problems, and an ECG had been normal, at least in 1974. He had a history of mild hypertension. It is of interest that the patient had an initial increase of LDH, CPK, and alkaline phosphatase, and normal SGOT and SGPT values. The increases in LDH and CPK values were accompanied by ECG changes. Within a few days there was a rapid rise of SGOT and SGPT values indicating possible liver necrosis as well as cardiac damage. His albumin-globulin ratio and bilirubin level remained normal. A liver biopsy was contemplated; however, the patient refused it. Abnormal levels of alkaline phosphatase, SGPT and SGOT have persisted, indicating persistent hepatic damage; LDH and CPK values have returned to normal. We have found no mention of hepatic toxicity in patients with lithium intoxication in the literature. The patient's thyroid chemistry values were normal. A transient exophthalmus was noted. Segal and coworkers[19] found that in a group of 100 patients treated with lithium, benign and reversible exophthalmus changes developed in 11 patients. These patients likewise had normal thyroid chemistry values.

High doses of lithium, together with alcohol and Tranxene, decreased food and fluid intake and increased fluid loss hastened, no doubt, the onset of intoxication by a potentiation of action in the case reported here.

Both therapeutic and toxic levels of lithium affect multiple organs and cause changes ranging from mild abnormalities to severe toxic-necrotic states, depending on the levels of the lithium ion present.[20] Chronic and heavy alcohol use can cause extensive metabolic changes and have toxic effects on many organs. Large quantities of alcohol have dual effects on the metabolism of other drugs, making alcoholic patients less sensitive to anesthetics, sedatives and tranquilizers. However, alcohol also interferes with the liver's ability to detoxify drugs and prolongs their effect and, perhaps, potentiates the sedative effect of alcohol.[21] Clorazepate, a benzodiazepine, is a depressant of the central nervous system that is metabolized in the liver and excreted in the urine. The pharmacology, indications for use, withdrawal symptoms, side effects and toxicity of this drug have been described extensively.[22] It can cause behavioral, neurologic, few autonomic (cardiovascular) and, rarely, hepatic reactions. Potentiation of action with alcohol and psychopharmacologic agents occurs.

An increasing number of studies focus on the high incidence of mixed affective states combined with alcohol, sedative and stimulant abuse.[10,14] Since many such patients are treated with lithium and antidepressant and other psychotropic drugs, this highlights the urgent need to understand the complex interactions of various drugs to avoid overdosage, multi-drug treatment and serious complications such as seen in the case reported here. The treatment of lithium poisoning has been outlined by Schou.[23] In our patient lithium was rapidly eliminated despite the high levels at the time of admission, indicating good kidney function. Dialysis was contemplated but not done because of the rapid fall in serum lithium levels and the improved clinical state. In retrospect it is felt that dialysis as well as serial studies of erythrocyte lithium concentration should have been attempted. Elizur and co-workers,[24] found a consistent correlation between elevated erythrocyte lithium concentration, clinical neurotoxicity and EEG changes in a patient with normal plasma lithium levels. They found that in patients who were neurotoxic erythrocyte lithium levels were elevated to 60 percent of plasma levels of the ion. Frazer, Mendels and associates,[25,26] found that correlations between concentration of lithium in the brain and concentration of lithium in erythrocytes were consistently higher than were correlations between lithium levels of brain and plasma. Therefore, erythrocyte lithium concentration or, more specifically, the erythrocyte-to-plasma ratio, may turn out to be a more sensitive indicator of incipient toxicity or clinical improvement in psychiatric patients than plasma lithium levels alone.

Summary

In a middle-aged man with depression, treated with high doses of lithium carbonate (2,700 mg a day) for ten days, lithium intoxication leading to semicoma developed. His serum lithium level was 7.6 mEq per liter. Possible contributing factors were (1) decreased food and fluid intake; (2) fluid loss; (3) alcohol; and (4) tranquilizer intake. The patient's condition responded to intensive care, forced diuresis and other supportive measures; however, sequelae persisted six months after discharge. Cerebellar and upper motor neuron symptoms, a myocardial infarct and liver

damage with persistently increased enzymes occurred.

The need for accurate diagnosis, appropriate selection of dosage and careful monitoring of patients taking lithium is stressed.

Familiarity with the pharmacology and toxicology of lithium is a matter of considerable importance. The potential toxicity of lithium and its narrow therapeutic-toxic range have been discussed.

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Salicylate-Induced Noncardiogenic Pulmonary Edema

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SEVERAL DRUGS when ingested in therapeutic or toxic amounts are known to precipitate noncardiogenic pulmonary edema.[1-6] Prostigmine[1] and alloxan[2] are two agents capable of producing this clinical syndrome in normally prescribed dosages, while heroin,[3] barbiturates,[4] propoxyphene[5] and methadone[6] have varying incidences of pulmonary edema when taken as overdoses.

There have been reports that salicylates may induce pulmonary edema when taken in toxic amounts.[7-9] This association, however, is poorly recognized. Recent editions of textbooks of medicine[10] and pharmacology[11] fail to mention noncardiogenic pulmonary edema as an initial manifestation of salicylate poisoning. Part of the reason may be that the case reports supporting this relationship have seldom ruled out a subtle cardiac cause of pulmonary congestion; hemodynamic data are documented in only one report thereby establishing normal pulmonary vascular pressures.[9]

We report here another case of salicylate toxicity presenting with pulmonary edema. Swan-Ganz catheter data excluded a cardiac cause. We suggest that this aspect of salicylism receive greater recognition to insure early diagnosis and prompt therapy.

Report of a Case

The patient was a 69-year-old man brought to the emergency room confused and severely short of breath. From his friends it was learned

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that he had been in poor health for three weeks, complaining of weakness and malaise, and had remained in bed with little food intake. During the 12 hours before admission, shortness of breath rapidly developed followed by dizziness, diaphoresis, and confusion. The patient said he had had no chest pain, symptoms of congestive heart failure, palpitations, loss of consciousness or choking episodes, and had not ingested any drug or toxin including ethanol, methanol, ethylene glycol and salicylates. He was a reformed alcoholic and had smoked two packs of cigarettes a day for 50 years.

On physical examination the patient was noted to be hyperpneic, respirations were 30 per minute, pulse was 102 beats per minute, blood pressure was 142/70 mm of mercury and temperature taken rectally was 37.9°C (100.2°F). He was oriented to time and person only. His chest symmetrically expanded with bibasilar rales and wheezes more notable on the right without evidence of consolidation. Findings on cardiac examination were unremarkable with normal venous pulsations.

Laboratory studies gave the following results: serum sodium, 140 mEq per liter; serum potassium, 3.4 mEq per liter; serum chloride, 114 mEq per liter; serum bicarbonate, 7.9 mEq per liter; serum glucose, 115 mg per dl; blood urea nitrogen, 41.8 mg per dl; creatinine, 1.5 mg per dl; serum acetone, negative; prothrombin time, 13 seconds with a 11.5 second control; serum hemoglobin, 16 grams per dl; leukocyte count, 12,100 cells per cu mm with a normal differential count; platelets, normal by smear; erythrocyte sedimentation rate, 3 mm per hour. Arterial blood gas studies (Denver elevation) showed a pH of 7.43, oxygen pressure (P_{O_2}) of 31 mm of mercury and a carbon dioxide pressure (P_{CO_2}) of 13 mm of mercury on room air. After placement of nasal prongs with 4 liters per minute oxygen flow, the blood gas values improved with a pH of 7.48, a P_{O_2} of 82 mm of mercury and a P_{CO_2} of 13 mm of mercury.

Serum albumin was 4 grams per dl; hematest of stool was negative; expectorated sputum Gram stain and culture showed no pathogens; blood cultures were without growth; results of thyroid function tests were within normal limits. A serum salicylate level in a specimen drawn nine hours after the patient presented to the emergency room was 54 mg per dl. A blood and urine toxicology screen was otherwise negative. The cerebrospinal

Figure 1.—Radiograph of the chest in a patient with pulmonary edema due to salicylate toxicity.

fluid was clear and contained no leukocytes, 30 red cells and normal levels of glucose and protein. The cerebrospinal fluid salicylate level (obtained within one hour of the blood level) was 21 mg per dl. An analysis of urine showed 1+ ketonuria; the electrocardiogram was normal except for sinus tachycardia; a radiograph of the chest showed bilateral alveolar infiltrates compatible with pulmonary edema (Figure 1).

A Swan-Ganz catheter was inserted into the pulmonary artery and the following initial pressures were obtained: pulmonary artery (PA) systolic pressure of 36 mm of mercury, PA diastolic pressure of 12 mm of mercury and a pulmonary capillary wedge (PCW) pressure of 3 mm of mercury.

Noncardiogenic pulmonary edema secondary to salicylate toxicity was diagnosed and forced alkaline diuresis was initiated. Vitamin K (10 mg) was given intravenously. Fluid therapy during the first 24 hours consisted of 4.4 liters of 5 percent dextrose and 0.45 percent saline, 176 mEq of sodium bicarbonate, and 120 mEq of potassium chloride. Urinary output during this period was 2.6 liters, and the pulmonary artery pressures were unchanged until 24 hours into therapy when the PA systolic pressure was 44 mm of mercury, the PA diastolic pressure was 18 mm of mercury and the PCW pressure was 5 mm of mercury. Administration of ampicillin (1 gram given intravenously every four hours) and gentamicin (100 mg given intravenously every 12 hours) was started empirically on admission but was stopped after 24 hours when cultures were negative.

This therapy resulted in a salicylate level of 29 mg per dl 24 hours after admission, falling to 16

mg per dl the following day. Coincident with the fall in salicylate level was clearing of the pulmonary edema and improvement of the arterial blood gas values to a pH of 7.43, a Po_2 of 76 and a Pco_2 of 24 on room air five days after admission. There was no electrocardiographic or creatine phosphokinase enzyme evidence for a myocardial infarction. A computerized axial tomographic scan of the head showed no abnormalities.

When the patient's mental status improved, he admitted to taking six to eight aspirins a day for multiple complaints but in the last two weeks had taken them "by the handful" because of increasing fatigue.

Discussion

The association of salicylates with pulmonary edema was first noticed in patients with rheumatic heart disease[12,13] and later in patients with normal cardiac function.[7-9,14] Reid noted that in occasional patients with active rheumatic carditis treated with salicylates pulmonary edema developed which responded to phlebotomy.[12] Sutcliffe reported the case of a patient with rheumatic heart disease in whom pulmonary edema was noted after each of two courses of salicylates in the absence of any evidence for cardiac failure.[13] Granville-Grossman first reported salicylate-related pulmonary edema in a man without known heart disease. However, the pulmonary edema occurred only after forced alkaline diuresis suggesting that volume overload may have played a role.[14] Subsequently, the cases of three salicylate-intoxicated patients were reported[7,8] who presented with pulmonary edema and no apparent heart disease or clinical evidence of congestive heart failure. Pulmonary capillary wedge pressures, however, were not obtained so that a noncardiac cause was poorly documented. Hrnicek's case report[9] was the first to document normal pulmonary vascular pressures in a case of salicylate pulmonary edema. In Anderson's review of 73 patients with salicylism, seven of the patients presented with pulmonary edema and in one of these hemodynamic monitoring showed a normal pulmonary capillary wedge pressure.[15]

Our patient was admitted with extreme hypoxia and pulmonary infiltrates considered to represent pulmonary edema. Aspiration pneumonitis could have mimicked the radiographic findings and clinical presentation. However, the absence of a history of aspiration or of visible vomitus, the rapid clearing shown on sequential chest radiograms without a course of antibiotics, and the absence of pulmonary pathogens made this diagnosis unlikely. The pulmonary edema was deemed noncardiogenic because of the low pulmonary capillary wedge pressure and salicylism was considered to be the primary precipitating factor because a fall in serum drug levels coincided with clinical improvement.

The mechanism by which salicylates induce pulmonary edema is uncertain. Increased plasma volume with resulting elevated left atrial pressure was suggested by Reid.[12] However, the findings of a low pulmonary capillary wedge pressure exclude this explanation. For the same reason the mechanism of salicylate induced "high output" failure suggested by animal[16] and human[17] studies lacks support.

Experiments in sheep provide evidence that salicylates may mediate pulmonary edema by damaging pulmonary vessel endothelium thereby increasing capillary permeability to fluid and protein.[18] Cannulated lymphatic channels draining the lungs of these animals show an increase in lymph flow and lymphatic protein content after intravenous infusion of acetylsalicylate. These events occur without accompanying changes in pulmonary vascular pressures. These results suggest that salicylates generated a capillary-alveolar membrane "leak" with transudation of intravascular fluid and protein into the alveolar space.

If pulmonary edema is produced through damage to pulmonary vascular membranes, the mechanism whereby salicylates generate these defects is speculative. Conceivably, they may directly stimulate the brain, triggering a massive sympathetic nervous system discharge similar to that postulated for neurogenic pulmonary edema.[19] In this schema the sympathetic stimulus may produce a pronounced but transient increase in pulmonary artery pressures which somehow alters capillary permeability. After the pulmonary edema is established, the vasospasm remits and pulmonary vascular pressures are low or normal.

Alternatively, it has been suggested that prostaglandins are involved in salicylate pulmonary edema.[18,20] Prostaglandins may play a role in the generation of increased systemic vascular permeability,[21] and may be involved in maintaining the integrity of the pulmonary microcirculation.[22] Salicylates, by inhibiting prostaglandin synthetase, may intercede unfavorably in prostaglandin bal-

ance and thereby disturb the membrane stabilization process. Support for this thesis exists in preliminary findings in animal studies which suggest that indomethacin (also a prostaglandin synthetase inhibitor) has aspirin-like qualities of increasing pulmonary lymph flow.[20]

In addition, platelets have been incriminated in the production of this syndrome. Human platelets have an endothelium protective role,[23] and since salicylates impair platelet function, capillary membrane support may be weakened.

Regardless of the specific cause of the pulmonary edema, it is important that clinicians be aware of this complication of salicylism because florid respiratory failure may obscure common clues to the underlying diagnosis. In the case presented here, there were clinical and laboratory points suggesting salicylate toxicity such as hyperpnea, disorientation, ketonuria, acid-base abnormality and prolonged prothrombin time. But in the setting of pulmonary edema these findings could have been attributed to hypoxia and resultant lactic acidosis, recent starvation and suspected alcoholism with impaired hepatic synthetic capabilities.

Recently, Anderson has shown that patients taking salicylates chronically may present with occult toxicity.[15] The mortality in these patients increases to 25 percent if the diagnosis is delayed. The case reported here underscores the urgency of recognizing the multiple fashions in which salicylism presents in order to diagnose it clearly and treat it rapidly. Noncardiogenic pulmonary edema must alert clinicians to the possibility of salicylate overdosage particularly when other clues to the diagnosis are obscured by respiratory failure.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

An Arthritis Consultation Clinic— A Method of Continuing Education

TO THE EDITOR: There are two points on which medical educators agree: (1) the best educational experience is one that actively involves the learner and (2) it is difficult to show that a program actually changes clinical practice. An educational venture, conducted for the past ten years in the Northwest, fulfills these two conditions and has relevance for other communities in the West.

Lewiston, Idaho, and Clarkston, Washington, are located on opposite sides of the Snake River at its junction with the Clearwater, 340 milest east of Seattle. In 1969, when the program was started, Lewiston had a population of 26,000 and Clarkston 6,000. The community has two general hospitals of 120 and 60 beds. In 1969 there were 40 doctors (there are now 70), including family practitioners, surgical specialists, a pathologist, a radiologist and three general internists, but no medical subspecialists.

In 1968 Wallace Douglas, MD, an orthopedic surgeon, decided that management of patients with rheumatic diseases could be improved. The program we initially devised is the one we have continued to follow, with very little change. Clinics are held on the first Wednesday in February, May, August and November. Announcements of date, time, place and visiting consultants are sent to local physicians by the Idaho Chapter of The Arthritis Foundation. When physicians who would like to refer a patient call for an appointment, they are requested to have appropriate laboratory test results and x-ray studies available. From the outset we insisted that the physician accompany his patient.

The clinic is held in one of the hospitals which provides a conference room, two adjacent examining rooms, and a nurse who meets the patients and prepares them for examination. Each physician briefly presents his patient's history to the consultant and others in attendance. The group then enters the examining room, where the consultant reviews salient points with the patient and demonstrates an examination of the joints. Patients with arthritis lend themselves well to group demonstration, since physical findings are readily and conveniently visible. All then return to the conference room, where x-ray films are reviewed, and the consultant presents a brief discussion, makes recommendations, and answers questions posed by the attending physician or other members of the group. Finally, he dictates a brief note for the patient's record.

All of this requires 20 to 30 minutes. The number of patients seen in one day has varied from 12 to 22, with an average of 15. The number of physicians in attendance has averaged ten, although not all stay for the entire day. Others at the clinic have included registered nurses, physical therapists, student nurses, student therapists, nurse practitioners and medexes.

Usually the consultant arrives in Lewiston on the morning plane, conducts the clinic from 9 to 12 noon and from 1 to 4 PM, and flies home that evening. Most of the rheumatologists in Seattle have taken part. With one exception, all have enjoyed the experience and found it rewarding, and many have made repeat trips.

Funding is provided by the Idaho Chapter of The Arthritis Foundation which pays the travel expenses (approximately $115) and an honorarium of $100. The hospital donates space and nursing help. We have chosen not to bill patients for this consultation, although this could be done.

Many innovative educational programs have been proposed or described as an initial venture, but the Lewiston-Clarkston Arthritis Consultation Clinic has continued on a regular schedule for ten years. This longevity is one measure of its success. The key to its viability is the local committee, whose chairman is the focal point for the medical community. He arranges the schedule and coor-

dinates the visit of the consultant. One of the things we have learned from this experience is that a consultation clinic cannot succeed without local initiative, regardless of the interest of The Arthritis Foundation or consultants.

With ten years of repeated visits by the same consultants, it has been possible to observe some effect of this program, as reflected by changes in actual practice that rheumatologists believe represent better care. For example, in the treatment of rheumatoid arthritis there has been more prolonged use of aspirin and less reliance on brief trials of corticosteroids, or of other nonsteroidal anti-inflammatory agents. Gold which initially was rarely used because of unfamiliarity is now prescribed regularly. The sedimentation rate has been introduced into the "rheumatoid panel" of laboratory tests. Joint aspiration for diagnosis is a more common procedure, and synovial fluid is tested for crystals and leukocytes rather than protein content.

When initially asked to take part, some rheumatologists were reluctant, feeling that the problems would be too complex to make a firm diagnosis or therapeutic decision in such a setting. This fear has proved unfounded. In ten years there have been no more than five occasions when it was appropriate to recommend that the patient be referred to an arthritis center for more extensive investigation. Consultants have been pleasantly surprised to find that the patients present stimulating and interesting problems, and it has been gratifying to learn that even though deprived of detailed laboratory testing, they can arrive at a decision and make recommendations to patient and physician.

The clinic of May 1978 was typical. It numbered 19 patients, including seven with rheumatoid arthritis and one who feared she had the disease. There were two patients each with osteoarthritis, lupus, the Reiter syndrome and fibrositis, and one patient with back pain, one with colitic arthritis and one with early scleroderma.

In summary, this is a description of a method of postgraduate education by means of a quarterly arthritis consultation clinic that has continued to meet for ten years. As measured by one rheumatologist spending a whole day to talk to ten physicians and six other health personnel, it would not be considered an efficient teaching device. From the standpoint of involvement of the learners, continued interest and demonstrated change in habits of rheumatologic practice, it is a demonstrably effective one.

LOUIS A. HEALEY, MD
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Anaphylaxis to Kissing Bugs

TO THE EDITOR: Recently, I talked with a very frustrated school teacher from the western Sierra foothills of California who had the misfortune of having progressively more severe hives and, later, anaphylactic reactions to kissing bugs (Triatoma). Kissing bugs are nocturnal bugs that must feed on mammal blood to mature, and are found in the low elevation foothills of the Sierra and the desert region of Southern California. The people affected are apparently allergic to the proteins in the saliva, as there is no venom. However, the end result is, in a few people, as serious as that from Hymenoptera stings.

The reason my patient was so frustrated is that she has more than once almost literally staggered into a hospital emergency room where the physician on call has told her that she is hyperventilating, or simply overly nervous, and that this is the reason for her hives, shortness of breath and mental confusion.

The treatment for this type of allergic reaction is the same as for any accelerated drug or insect reaction: administration of adrenalin, antihistamines and corticosteroids as needed to suppress the symptoms, with use of cardiorespiratory resuscitation techniques if the patient's condition becomes that severe.

With increasing numbers of people moving to the high desert and Sierra foothills, there are very likely to be increasing numbers of people affected by these reactions, which characteristically come on in the middle of the night with the person waking up itching and scratching as hives occur. This progresses to shortness of breath with asthma and even changes in voice as laryngeal edema occurs.

Patients should be provided with insect sting kits consisting of an adrenalin syringe, preloaded and ready to use, and chewable antihistamine tablets. They should be instructed to use the adrenalin and the antihistamine and then go to an emergency room. Use of whole body Triatoma extract has been suggested by a few allergists, but there is no proof that such treatment is effective and the recent experience with whole body insect

extract casts doubt on the possibility that this could be effective.

One death from this type of allergic reaction has been recorded in a newspaper (*Merced Star,* May 31, 1975). With growing numbers of people exposed to this problem, research is urgently needed. Until effective preventive treatment is developed, the least we can do is to make sure that all emergency room physicians are aware of the problem. There is a kissing bug and it does cause severe allergic reactions including anaphylaxis.

ROBERT W. MONTGOMERY, MD
Visalia, California

Legionnaires' Disease

To the Editor: Legionnaires' disease was discussed by Dr. Barbara Kirby in the Medical Staff Conference in the December 1978 issue. It essentially was a review of material previously published by her and her colleagues.[1]

She stated that Legionnaires' disease has not been seen in Los Angeles apart from the Veterans Administration Wadsworth Hospital Center experience. We as a group of three pulmonary practitioners in private practice have discovered 14 cases in four different hospitals in the San Gabriel Valley of Los Angeles County in the last 11 months which meet the Center for Disease Control (CDC) criteria for either a presumed or a confirmed case.[2,3]

Although Dr. Kirby feels that there is a characteristic symptom complex, this has not been our experience. We are unable to separate the clinical presentation of Legionnaires' disease from other infectious pneumonias. Perhaps the sporadic nature of our cases over a large geographic area which conceivably may involve several serotypes might in part explain this difference.

We do not understand her statement that there is not an easy reliable method for diagnosis. In both the CDC's and our experience, the immunofluorescent antibody test has been an easily performed, reliable test. For the last year it has been commercially available through the Analytical Reference Service in Long Beach, California, with results being reported to the clinician in 48 to 72 hours. Initially we had split our specimens and sent one to this laboratory and one to the CDC. Because both laboratories reported the same titer we have stopped sending specimens to the CDC which requires 6 to 8 weeks turnaround time. The most pressing current problem with this test is to incorporate enough of the serotypes to detect all clinical cases.

Doctor Kirby commented that pulmonary cavitation is not seen on x-ray films of the chest. As is so often the case, the more a disease is recognized, the broader its spectrum of clinical manifestations. We have recently observed two cases of Legionnaires' disease with cavitation.[4]

Our experience would suggest that this is not an uncommon disease, that a reliable rapid test is available for diagnosis, and that in patients with pneumonia, physicians should consider Legionnaires' disease when the cause of the pneumonia is not obvious.

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PETER M. BROWNE, MD
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* * *

Dr. Kirby Replies

To the Editor: Dr. Lake and his associates state that the Medical Staff Conference "essentially was a review of material previously published." The conference was held in August 1978, before any detailed publication of the Wadsworth experience. At the time of the conference, 51 cases of Legionnaires' disease had been reported in Los Angeles County; in 49 of these cases exposure to Wadsworth Hospital was documented.[1]

I cannot comment on whether or not the 14 patients mentioned by Dr. Lake and associates had Legionnaires' disease because no data are presented. I would urge any physician who thinks he has diagnosed even a single case of Legionnaires' disease to report it promptly to the appropriate public health authorities so that epidemiologic studies may be undertaken. One of the striking features of Legionnaires' disease is its frequent association with specific buildings and geographic areas. With effective therapy available, early identification of such sources and notification of local physicians may prevent needless morbidity and even death.

As stated in the Medical Staff Conference, Legionnaires' disease at Wadsworth hospital has presented as a readily recognizable clinical entity.

Certainly no single finding is diagnostic, and, as in any disease, a clinical spectrum can be expected to emerge with some patients presenting atypically.

It is extremely important that any physician attempting to diagnose and treat Legionnaires' disease has a fundamental understanding of the appropriate use and application of the indirect fluorescent antibody test. It often takes three weeks, and may take six, for diagnostic rise in antibody titer to occur. A negative titer early in the illness *is the rule.* A positive titer (unless accompanied by a fourfold rise $\geq$1:128) early in illness may, in fact, represent remote, not current infection. Because Legionnaires' disease may be rapidly fatal unless specific therapy is instituted,[2,3] one cannot wait for diagnostic seroconversion to occur, nor should therapy be withheld based on the initial negative titer. My statement was "there is not an easy reliable method of diagnosis *during the acute illness*" (emphasis added). Although newer methods are emerging that may permit early diagnosis, the indirect fluorescent antibody test clearly is *not* one of these.[4] The rate limiting factor is the patient, not the laboratory.

In the past few months, several investigators have noted pulmonary cavitation in association with Legionnaires' disease. This unusual manifestation has still not been seen at Wadsworth.

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Medical Quality Review Committees in California

To the Editor: In the Information section of the November issue Samuel E. Spital, Esq. in his article "Understanding Physicians' Rights and Liabilities Under the California Medical Practice Act" makes a significant omission in his enunciation of the steps in the administrative process of a disciplinary hearing by the California Board of Medical Quality Assurance. There is not, as he implies in his article, an automatic assignment by the Office of Administrative Hearings of a case to an administrative law judge to hear and decide. Local Medical Quality Review Committees were created by the legislation to function at the local level and may, at their discretion, be assigned the case by the Office of Administrative Hearings. The local boards of Medical Quality Review Committees, 14 of which have been established on a geographical basis, are to ensure that there is local input from both physicians and consumers in the disciplnary process and to extend the reach and effectiveness of the Division of Medical Quality.

The committees range in size from 10 to 40 members and consist of physicians, allied health professionals and public members. They have the responsibility of providing meaningful quality assessment and peer review at the local level. Their decision in a case may then be subject to administrative review by the Division of Medical Quality on appeal by the physician concerned.

Medical Quality Review Committees also work to identify local health care problems and are currently assessing a wide range of topics including drug abuse, physician alcoholism, improper use of emergency rooms by the public and inferior quality of emergency room care by physicians, among topics.

JOHN B. WELSH, MD
Member, Fourteenth District Medical Quality Review Committee
San Diego

Another Cowboy Selling Cancer

To the Editor: On nationwide prime-time television sporting events, an ex-football player/cowboy star demonstrates the proper technique of "dipping" moist or Copenhagen variety snuff tobacco by placing a pinch of the flavorful economical substance in his lower gingivobuccal groove. However, the commercial neglects to point out that prolonged "pleasurable dipping" can lead to large ulcerating, fungating squamous cell carcinoma at the site of application.

With the advent of uncontrolled national television advertising of this form of tobacco, the habitual use of snuff may become popular nationwide. Before television, the consumption of snuff tobacco was greatest in the South, although appreciable amounts were used in the North Central and Northwestern States.[1] A Tennessee study described "snuff dipper's cancer" in male and female habitual users of snuff.[2] Of female patients with gingivobuccal squamous cell carcinoma, 90 percent were habitual users of snuff. This rare in-

sidious type of carcinoma is devastating and often requires extensive oral or neck surgical operation, or both.

The American Cancer Society, medical associations and officials of the Department of Health, Education, and Welfare have mounted extensive antismoking campaigns to convert cigarette smokers to total abstainers. In contrast, none of these groups recently have pointed out the dangers of "dipping" snuff. Although "the Surgeon General has determined that cigarette smoking may be dangerous to your health," no mandatory hazardous tobacco notice is required on either snuff cans, magazine advertisements or television spots.

Now is the time for the medical community to point out the danger of "pleasurable dipping." Before an "I Quit" campaign is necessary, an appropriate effort must be instituted to counter another cowboy selling campaign.

HOWARD H. FRANKEL, MD, PhD
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Autoimmune Therapy for Herpes Zoster

To the Editor: In the December 1978 issue there appeared an excellent article by James B. Reuler on herpes zoster. In the section on therapy, however, he failed to mention a technique that has been in widespread use for many years. The technique for treatment may date back as much as 50 years, and has been called autoimmune therapy. For the past 25 years or more we have found it to be an effective form of treatment for acute herpes zoster. Several hundred patients have been treated in this manner and results have been consistently better than those obtained with any of the other methods of treatment to date. The technique consists of injecting 20 ml of the patient's whole blood (obtained by venipuncture) into the buttocks, 10 ml being injected into each buttock. This is usually done daily for three to four days or it can be done every other day for approximately three times. The herpetic lesions begin to dry up within 24 to 48 hours. This is accompanied by a lessening of symptomatology. There have been no side effects as observed with this treatment to date. I shall not expound the theoretical basis for this therapy due to a limitation of space.

RONALD M. LAWRENCE, MD, PhD
North Hollywood, California

* * *

Dr. Reuler Replies

To the Editor: Dr. Lawrence describes an interesting form of therapy for herpes zoster which I had not seen discussed in the literature. Many therapeutic modalities, varying from administration of cobra venom to use of influenza vaccine, have been reported to be successful in the treatment of herpes zoster. However, none has been universally accepted as efficacious. It is important to bear in mind that herpes zoster is usually a self-limited disease, the clinical course of which is relatively brief and without sequelae. Therefore, to ascribe the rapidity of clinical improvement or a decrease in complications to a particular therapeutic regimen demands that a controlled study be undertaken. To date, only idoxuridine in dimethyl sulfoxide, corticosteroids, adenosine-arabinoside (ARA-A) and human leukocyte interferon have proven efficacious in such critical analyses.[1-4]

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Control of Plague

To the Editor: We would like to comment on some points in the otherwise excellent Specialty Conference on plague in the November 1978 issue. It was stated that after identification of the campgrounds where the San Diego girl probably contracted her plague, "exterminators" went in to "reduce the infected animal population." Not so; such action would make matters worse because infected fleas would then abandon those hosts and attack others, including man. Rather, measures were taken *with insecticides* [by the state's Vector Biology and Control Section (VBCS), aided by United States Forest Service personnel] against vector fleas in order to break the chain-of-infection among sylvatic rodents and between rodent

fleas and man. Control measures include selective dispensing of an effective insecticide dust with hand dusters into burrows, dens and nests. Sometimes, insecticide-bait stations are also set up for rodent self-application. Such flea control is the most rapid, economical and effective means to break the chain-of-infection and to protect persons using such areas. Animal extermination is not used by the state Department of Health Services or by the United States Public Health Service.

In addition to responding to outbreak situations, there is an ongoing statewide program in California for the surveillance and suppression of plague conducted by the VBCS. Whenever areas with evidence of plague activity are judged to present a risk to humans, the areas are promptly quarantined, warnings are posted and suppressive measures are undertaken with insecticides to control flea populations.

We view plague as a public health emergency. Rapid laboratory diagnosis of cases in humans is essential and, according to state regulations (Sections 2501 C and 2596, California Administrative Code, Title 17), the state Department of Health Services is to be notified immediately of all suspected cases of plague to expedite laboratory, epidemiologic, and field investigations. The identification of Yersinia pestis in the hospital laboratory by biochemical and other tests is too slow a process. Accordingly, we urge California physicians and laboratory directors to consult promptly the state's Microbial Diseases Laboratory which can quickly perform fluorescent antibody procedures, phage tests, and animal inoculations of specimen materials or suspect cultures.

The authors emphasized that "domestic (urban) plague is not a thing of the past" by pointing out that as recently as 1968, "domestic rats" in Denver were identified as infected with plague. We have no quarrel with the concept that urban plague can erupt from commingling of sylvatic and domestic rodents, but the authors should be more precise: the infected Denver rodents were not "domestic rats"—they were tree squirrels.[1] And despite the statement that an outbreak in humans was averted by a "rodent control program," a human case did occur.[1] Actually that case was identified before the epizootic in squirrels was recognized; and to control that epizootic, measures were taken against the fleas, not the squirrels. The Denver situation provides us the opportunity, however, to emphasize that with the encroachment of urban/suburban growth on previously sylvan areas, peridomestic sylvatic rodents may become as important a threat of plague transmission to man as domestic rodents were in the past.

Finally, we wish to correct for the record the statement that the fatal case of plague pneumonia in 1977 contracted by a California veterinarian resulted from his autopsy of an infected dog carcass. We investigated that case along with the Santa Clara and Monterey County Health Departments and could identify no definite source of infection: he was not known to have performed any recent postmortems, nor had he had any known flea bites or contact with animals with respiratory symptoms; he had also not camped anywhere. His clinic was in an area with a documented history of previous plague epizootic activity. While we can *speculate* that he inhaled or swallowed an infected flea (or its vomitus) from one of the cats or dogs he tended, or even a sick ground squirrel, it is far from certain that this was the source of his infection. We would prefer to report the source as unknown.[2]

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Cardiopulmonary Resuscitation in Patients Over 65

TO THE EDITOR: I believe the impact of cardiopulmonary resuscitation (CPR) on patients over 65 is often maleficent.

May I comment on Dr. Richard L. Coskey's careful report in the December 1978 issue (Cardiopulmonary Resuscitation: Impact on Hospital Mortality—A Ten-Year Study)? In older persons, it is my opinion that when more than five minutes is required to reestablish a viable heart rate and rhythm, the impact of CPR is more often harmful than helpful. Table 1 of Dr. Coskey's article seems to substantiate my conclusions. It reveals

that for 1973 and 1974, resuscitation was carried out in 165 patients of all ages. Even in this younger (on the average) group "increasing instrumentation" *prolonged the act of dying for 57 persons and left 16 others to exist with brain damage.*

I have studied 46 consecutive "successful" resuscitations *in patients over 65* at Peninsula Hospital and Medical Center, Burlingame, California. Of the patients, 63 percent died of their underlying disease before they left the hospital. In other words, their act of dying was prolonged.

My personal survey of internists over 65 reveals that 50 percent, in the event they suffer an instantly observed and treated "arrest," would disapprove of CPR lasting more than five minutes for themselves. If they so desire, means are available to let our sapient patients in this age group make the same informed decision. A modified living will[1] can do just this.

I would be greatly interested in Dr. Coskey's figures for his patients over 65. I hope they are not as melancholy as those from three Nurnberg hospitals who reported in 1976 that 239 patients over 60 were resuscitated "successfully." At the end of six months, only nine were alive.[2]

I believe many patients would consider this impact on their lives as summun malum.

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* * *

Dr. Coskey Replies

TO THE EDITOR: Dr. Baer's letter reflects concern regarding possible brain damage in a patient who has otherwise undergone successful cardiopulmonary resuscitation (CPR). In our study 4 percent of all patients resuscitated had brain damage (as was shown in Table 1).[1] Patients 60 years of age or older, a total of 776 in number or 67 percent of the total 1,155 patients, had the same 4 percent incidence of brain damage as did the total group.

No time limit should be placed on CPR.[2,3] A four- to six-minute time interval might be considered if it were known that CPR was not appropriately applied and there was inadequate maintenance of cerebral blood flow. With correct application of CPR, adequate cerebral perfusion can be maintained for prolonged periods of time to prevent brain damage.

It is important in reviewing the 1973 and 1974 statistics (Table 1 of the article in the December issue) to point out that 92 patients *did not die* even though a lesser number did succumb to their underlying illness before hospital discharge. Few patients with brain damage live to see hospital discharge.[4,5]

The incidence of survival following CPR is inversely related to age. Nevertheless, 20 percent of 156 patients 60 years of age or older in this ten-year study were long-term survivors.

The data from the three Nurnberg hospitals[6] were indeed melancholy. Seven percent of the total group of 335 patients, or 24, were discharged from the hospital. Their data base is slightly different in that they only tabulated patients whose resuscitation lasted at least four minutes. Nevertheless, I would hope that, with experience and time, improvement will be noted, as was portrayed in Figure 1.

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Sex Education for Teenagers

TO THE EDITOR: The views of the Special Editor for Idaho, E. R. W. Fox, MD, in the November issue, "Sex Education for Teenagers," were most provocative. Dr. Fox suggests that physicians have been reluctant to advocate "family planning and sex education" (translation: contraception counseling) for teenagers for various and sundry reasons. Among these: because we "feared rebuff," "felt unqualified for lack of learning," "were not comfortable in dealing with this sensitive subject." I would challenge his explanations, and suggest that physicians have considerably more reason and justification for their reluctance than his essay would suggest.

Dr. Fox fails to consider, at all, the fact that many physicians may have "reneged" on their alleged "responsibilities" because they are really quite convinced that *this* approach is *itself* quite irresponsible. In fact, they may feel that his approach will do more harm than good, in the sense

of encouraging even greater teenage promiscuity, thereby, ultimately, aggravating the problem of premarital teenage pregnancy. In fact, considerable factual evidence can be cited in support of such a notion.

The first thing to note is that during the past five years, family planning agencies have made great strides in reaching more teenagers than ever before, with more of their services. The number of teenagers in organized family planning programs quadrupled between 1970 and 1975, from 300,000 to 1.2 million.[1] Abortion became legal and widely available to teenagers. Instruction in the use of contraceptives became a normal (even though unofficial) part of the curriculum in sex education courses all across the country. While it might have been possible in 1971 to claim that only a small proportion of the teenage population found contraceptive information and services available, this was simply not the case five years later.

It would seem reasonable, then, if Dr. Fox's thesis is correct, to expect a decline in teenage pregnancy and childbearing during this period. But the findings of Kantner and Zelnik, for example, show just the opposite.

In their 1971 study, 6.4 percent of the girls interviewed had had a premarital pregnancy.* By 1976 this proportion had jumped to 9.3 percent, an increase of 45 percent.[2] This was obviously related to a nearly equal increase (41 percent) in the percentage of girls who had had premarital intercourse, from 26.3 percent in 1971 to 37.2 percent in 1976.[3] The rate of out-of-wedlock births, despite the legalization of and widespread recourse to abortion, increased from 10.3 per 1,000 in 1971 to 12.1 per 1,000 in 1975, up 18 percent.[4] And even if we take into account the increase in sexual activity among teenagers, and consider only the rate of premarital pregnancy among those who were sexually active, *there was still an increase* of about 4 percent, from 24.3 percent in 1971 to 25.2 percent in 1976.[2]

Zelnik and Kantner themselves admit to having a little difficulty with this anomaly:

> If all other factors had remained the same, the substantial increase in the prevalence of premarital sexual experience among teenage women between 1971 and 1976 might have been expected to result in an increase in premarital pregnancy. Over the same period, however, these same young women reported a dramatic increase in overall contraceptive use, in use of the most effective methods, and in more regular use of all methods—changes which, other things being equal, should have led to a decrease in premarital pregnancy. . . . The lack of decline is somewhat surprising in light of data previously presented on changes in contraceptive practices.[5]

Those changes in contraceptive practices were significant indeed during the five-year study period. In 1971 only 19.7 percent of the sexually active girls had used a contraceptive every time they had intercourse. By 1976 this had grown to 30.2 percent.[6] Perhaps more significant, fewer than half the girls in the 1971 sample (45.1 percent) had used a contraceptive on their last sexual encounter before they were interviewed. In 1976 almost two thirds (64.8 percent) had,[6] and they were using the most effective medical methods of contraception. In 1971 only 13.8 percent of the sexually active girls were using birth control pills or intrauterine devices (IUD). This percentage more than doubled by 1976, to 33.3 percent.[7] Zelnik and Kantner had good reason for expressing surprise at the "lack of decline" in teenage pregnancy. This "lack of decline," let us recall, is actually an increase.

But the ineffectiveness of contraception for teenagers is something that has been well known at least since 1973, when Ryder published his study showing that the failure rate among young women using oral contraceptives was four to five times higher than that among older women.[8] And when this fact is read in light of the earlier study by Ryder and Westoff,[9] showing that even older, married women are none too successful in preventing unintended conceptions, the situation appears even worse.

In view of these findings, of which every advocate of the contraceptive approach should be aware, it would seem irresponsible to teach teenage girls that they can reliably avoid pregnancy by using the contraceptive approach.

There are some, like Dr. Fox, who look upon contraceptive programs for teenagers as an alternative to abortion. But Kantner and Zelnik inadvertently show how illusory is the hope of reducing the so-called "need" for abortions by giving teenagers contraceptives. They compared the percentage of contraceptive users among those girls who obtained an abortion with the percentage of contraceptive users among those with some other pregnancy outcome, and found that "those young women having an abortion are seen to be

*Here and throughout, I am citing Kantner and Zelnik's figures for "white" teenagers (which includes all nonblacks). This is because, by their own admission, their figures for blacks are neither internally or externally correlatable, and because the data for "whites" display trends more clearly.

almost twice as likely to have been contracepting at the time pregnancy occurred."[10] In other words, girls who become pregnant while using a contraceptive are more likely to seek abortion than those who become pregnant without using a contraceptive.

So, far from being an alternative, family planning programs for teenagers are an inducement to abortion. They help to build a new clientele for the abortion clinics.

Perhaps Kingsley Davis said it all, and said it most succinctly, in his report to the United States Commission on Population Growth and the American Future:

> The current belief that illegitimacy will be reduced if teenage girls are given an effective contraceptive is an extension of the same reasoning that created the problem in the first place. It reflects an unwillingness to face problems of social control and social discipline, while trusting some technological device to extricate society from its difficulties. The irony is that the illegitimacy rise occurred precisely while contraception was becoming more, rather than less, widespread and respectable.[11]

It would not be possible, on the basis of the available data, to state categorically that the current increase of promiscuity among teenagers is directly and solely caused by the increased availability of contraception and abortion. However, this must be considered a most likely causative factor since this was the chief pertinent variable in the sexual environment of teenagers in the five-year period under discussion. Dr. Robert Kistner of Harvard Medical School, a developer of the oral contraceptive, lent his support to this hypothesis in speaking to the American College of Surgeons in December 1977: "About ten years ago I declared that the pill would not lead to promiscuity. Well, I was wrong." *(Family Practice News,* Dec 15, 1977, p 1.)

Kistner's about-face on this question was prompted by his own experience in treating a steadily increasing number of young pill users for venereal disease and cervical canver, both of which have been linked to sexual promiscuity. Kistner asserts that the introduction of birth control pills has been a major causal factor in the rapid increase in both venereal disease and cervical cancer among adolescents by stimulating higher levels of promiscuity.[12]

For generations, parents taught their children moral responsibility and gave them the foundation on which to build their own families. This system was not perfect, but it produced better results than the current programs. It gave children reasons for preserving their chastity, and it supported them in doing so until they were mature enough to make responsible use of their sexual faculties. Parents could still do that. Indeed, many parents still are doing it, in spite of the general permissiveness around them. But if parents are to be effective in giving their children the moral training they so desperately need, they will have to be supported, not undermined, by government agencies, the medical profession and society at large.

We see few people nowadays suggesting that teenagers can control their sexual impulses, or that they might want to. Nor do we see very many of our opinion leaders applauding the ideal of self-mastery, or suggesting that we encourage such an ideal in our young people. (Even Freud, although he felt unconscious repression was harmful to the psyche, did not negate the value of sublimation or conscious suppression of impulses.)

Instead, it is becoming more and more apparent, as one views the passing scene, that some of the most respected elements in our society are, today, directly or indirectly, bent on encouraging teenage sex, and then hypocritically decrying the quite predictable results.

Advocates of the contraceptive approach have been known to scoff at those who favor chastity as the better "solution." Ironically, even while abstinence is ridiculed and the difficulties of chastity are increasingly exaggerated, efforts to explain away the deficiencies of the contraceptive approach (as noted above) are foundering.

Furthermore, the fact that parental and societal efforts to encourage chastity fall short of a perfect solution (and currently seem much less adequate than in previous years) should not cause us to lose sight of the fact that a great many teenage girls are still using abstinence, and, as a result, have not become pregnant. Were it not for them, the problem of premarital pregnancy would have been far greater than it now is. And it should be noted here that these teenagers have achieved and maintained this difficult and remarkable ideal in the face of a milieu that is not only pervasively unsupportive, but often actually hostile, toward the ideal of chastity.

In this context, I would emphasize Zelnik and Kantner's finding that 60 percent of the teenage girls in their study used abstinence as a method of pregnancy prevention.[13] Using this approach, these girls ran a *zero risk* of becoming pregnant. This fact alone suggests the wisdom in advising

all teenagers that abstinence is the only completely reliable method of pregnancy prevention for them.

But then, if we are to succeed in selling more teenagers on the value of chastity as the more reliable method, it will obviously be necessary to begin emphasizing the risks of failure in contraceptive usage, rather than falsely promising contraceptives as an easy escape from the natural consequences of premature, irresponsible sexual activity.

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Dr. Fox Replies

To the Editor: The thoughtful comments of Dr. Ford deserve consideration. It becomes quite obvious that he and I share many of the same convictions.

Unfortunately, the title "Sex Education for Teenagers" did not accurately portray the meaning of my correspondence. My contention, simply stated, was that we doctors, who by definition are supposed to be leaders and teachers, could be doing—and should be doing—a better job of leading and teaching in our communities. We have done a creditable job in teaching about athletic injuries. We willingly espouse programs for immunizing our younger generation. And yet, we draw back when it comes to dealing intelligently and unemotionally with teenage sexuality.

Dr. Ford and I are again in total agreement when we express a hope for a resurgence in morality, for a return to love with commitment and for a return to a high value of the family unit. As a father and a grandfather I know that most young people will, when given honest answers and straightforward information, hold to these simple values. And we, as physicians, should accept our share of the obligation to supply this information.

And so we come to the bottom line: 1 million teenage pregnancies a year, and almost 400,000 teenage abortions. These are distressing facts. Any physician who cares for pregnant teenagers is dismayed and saddened by their lack of knowledge in these matters so vital to their future mental and physical health. Someone sagely remarked that "getting pregnant doesn't require much knowledge, but not getting pregnant does." Haven't we in the medical profession always contended that we want our patients to be knowledgeable about the total health of their minds and their bodies?

If we as parents have been lucky enough to bring our sons and daughters through their teenage years without mishap, we still should not be blinded to the fact that there must be widespread sexual activity if we are confronted by 1 million teenage pregnancies each year. It follows that if we would deny a person access to contraception, then we must support the termination of life by abortion.

Somewhat to my surprise, the several letters I have received in regard to my comments in The Western Journal of Medicine were from women, all of them doctors' wives, and all mothers of teenagers. They all chorused the same sentiment: "Right on!"

Could there be a message here for us male physicians, husbands, fathers?

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Refer to: Dozier DF Sr: Geriatrics in practice (Commentary). West J Med 130:277,279, Mar 1979

Commentary

Geriatrics in Practice

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DR. ALEX COMFORT'S article[1] and Dr. Malcolm Watts' editorial[2] in the March issue of THE WESTERN JOURNAL OF MEDICINE were splendid and most timely discussions of geriatric medicine, an area with rapidly increasing problems—medical, social, sociologic and economic. Since 1923 as student, intern and longtime family doctor I perforce learned many things about clinical geriatrics.*

Few doctors choose to become geriatricians, or elect geriatrics as a specialty. Many of us after many years of general or specialty practice, without planning or forethought, become aware that an increasing number of our patients have evolved us into, at least part-time, geriatricians. As your practice, your patients and yourself grow older, geriatrics daily becomes more manifest. Usually age and experience enable a doctor to become fairly competent in this field in which the rewards are often more spiritual and intellectual than monetary. The trust and respect, the loyalty and affection, the goodwill and friendship of your older patients can go far to make your own Indian summer richer and more prideful. To our younger colleagues in many disciplines the following thoughts and suggestions are offered in the hope that some may find them of value as their patients, their practices, and their own corporeal changes march into the coming decades.

Those who survive the medical and surgical conditions of infancy and childhood, and as adults in an age of increasing stress eventually emerge into the "senior citizen" class surprisingly do not *usually* raise the challenging problems of diagnosis and treatment which occur in the younger ages. Another way of putting this is that if one can survive the first 50 years and more, diagnostic problems of the 60's, 70's and 80's—again *usually*—are not so difficult. Certainly each one of these several groups have their problems which inexorably worsen with the years—arthritic, diabetic, peptic or colonic, oncologic, hypertensive, psychosomatic and borderline psychiatric (for want of a better term) problems, and the various sclerosis and other "-osis" genera of which we are more and more aware. And, too, they have acute medical and surgical problems superimposed on their major malady. However, the vast majority usually "just go cookin' along" for many years, albeit the path be ever downward. And it is here that our efforts and advice may make those paths easier and kinder.

Our problems in geriatrics are more often in the realm of treatment and management. Somewhere between the frigid determination to "never go to a doctor" and "always running to the doctor" there is a role in which doctors can and should function. Services rendered will be worthwhile and valued by both patients and families. It is particularly regarding the doctor-patient-family relationship that I wish to offer some ideas and suggestions.

Above all if a physician has, regrettably, no empathy for geriatric patients, this should be admitted and a technique developed for graciously referring aged patients to doctors who will and do treat them. Many younger physicians, especially internists and family practitioners recently trained in the new holistic orientation, welcome such referrals and both a patient and the family appreciate the thought and effort in your having made the referral.

Geriatric patients often need, take and demand more time than younger persons; their complaints are more numerous or vague, their loquacity greater and more determined, their comprehension often slowed, and their resistance to change in orders or management frequently more determined. To get through an office visit in less than 40 minutes sometimes takes great tact and skill.

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"Going to the doctor" may well be the biggest thing in the daily life of some quite elderly patient. It is his or her hour to shine and be important in a world which to them is diminishing; to get batteries charged for another go at family or institutional life; to get new ammunition with which to maintain courage and stature in a relentlessly shrinking environment.

As routine and seemingly futile as an office visit may appear to be at times, it calls for great empathy and authority in the true meaning of these words. In most instances it can and should be rewarding to patient, family and medical attendant. Any sign of boredom ("He's losing interest.") may well lead to the basic failure of an office or bedside visit. Remember, the waiting rooms of health cultists and racketeers are often full of people who have first tried going to reputable members of the medical profession.

To really win the trust and loyalty of patient and family the physician should show them and explain the laboratory report, read and interpret the x-ray findings for them and not hesitate to show actual x-ray films, especially if they show no abnormalities. Very often visual evidence helps greatly in enforcing awareness of what has just been told to the patient and the few extra minutes may be of great value in reassuring or managing an insecure or apprehensive elderly person. In so many instances to have a secretary or nurse tell a patient over the phone that "the reports are all right" is to render an actual disservice, with scant help to the patient and no boost to the doctor-patient relationship.

Keep medications few and simple. Often it is wise to submit a written (legible) memorandum of your orders. When one learns of drug bills of $100 or more per month, take stock and find out what is going on. Unfortunately often it will be found that much of this money is going for mega-vitamins or over-the-counter nostrums which are outrageously priced and relatively worthless. It takes tact and skill to wean some of these older patients from such overpriced and ill-advised concoctions. However, it is often possible to introduce standard approved preparations in much smaller and safer dosage. This is particularly true of many vitamin preparations.

Sedatives, tranquilizers and soporifics should be held to a strict minimum both numerically and as to dosage. Try as tactfully as possible to see that such medicaments are administered by some member of the family and not left in the possession of the patient; remember that these patients "sometimes forget." Actually laying out the day's medicines and establishing a checkoff system may be of value in preventing abuse or overdosage.

Today in many communities licensed physiotherapists or qualified physiatrists are available. Especially for patients with arthritic or other somatic aches and pains, skilled and periodic use of properly selected physical therapy modalities may be of considerable value. Appropriate traction apparatus with adequate instructions may be used at home with appreciable benefit. Often a well-chosen modality may actually lessen the need and use of large doses of analgesics. Without expecting cure many old people will be most grateful for the relief and the care. And results achieved by a skilled therapist in cases of impaired function sometimes are amazing.

Be aware of and do give advice concerning those mechanical and physical factors that can do much to improve an elderly patient's comfort, convenience and mobility. We are living today in an era of low (and I do mean down low) furniture, automobiles and other devices that for all ages are awkward or hazardous to get into, and always more difficult to get out of. Getting many of our 70- or 80-year-old citizens into and out of one of our modern "igloo" automobiles sometimes is a real problem. Put the television set at eye level or a bit higher, thereby lessening the aching or pain from prolonged flexion of the upper portion of the cervical spine—and it may help the oldster to stay awake a little longer. Put 4- or 6-inch blocks under each corner of modern, low beds; the hazard of falling out of bed is far less than the threat of a compression fracture of an osteoporotic vertebra in the desperate struggle of some octogenarian to rise from one of these infernal beds that has a mattress no more than four or five inches from the floor. I urge you to see that your waiting room has at least two chairs of standard height—and preferably they should be armchairs.

When closing an office visit with a bit of discussion and advice, have a spouse, a daughter or son, or some responsible adult present. How exasperating it is, after some little time and effort on your part, to learn that when asked later what the doctor had said your patient answered "Oh, nothing." Believe me, a family witness to your remarks may be most helpful.

Dietotherapy should not be too strict or too lenient. Your advice to "eat whatever you want"

is sometimes interpreted as lack of interest—or lack of skill. In general, patients are appreciative if you discuss with them their own particular relationship to salt, carbohydrates and cholesterol-containing foods. When indicated, suggestions for substitutes are also greatly appreciated. (There are some really quite tasty soy bean substitutes for cow's milk on the market. I know.) But in many instances it is important to emphasize to patients that an occasional serving or taste of a forbidden food is not going to result in disastrous consequences. When appropriate, my own advice has been "I can give you a diet in ten words—*fresh* meat, fish, fowl, dairy products, vegetables, fruit simply prepared."

Consultation should be sought when conditions change for the worse; or when uneasiness or dissatisfaction become apparent in a patient or members of the family. Whether warranted or not, set things straight by asking for consultation: "When you are right, you welcome consultation. When you are wrong, God knows you need it." A skilled consultant can often be of great help in making families appreciate your efforts. If a patient or family wishes a consultant who for a number of reasons may not be proper for the case, the attending physician always has the right to name two or more other doctors who he feels would serve the interests of patient and family better.

Some oldsters may react with hurt, anger or improper sense of rejection if the attending physician suggests consultation. This is especially true if psychiatric consultation is sought. Our present generation of old people are not oriented to the value of expert psychiatric opinion and advice, and are greatly affronted if the suggestion comes from the doctor in attendance ("He thinks I am crazy.") and the old person will carry to the grave the hurt and anger. There are often times when it is wise to have the suggestion for consultation of whatever kind come from a member of the family or a colleague. This might seem an evasion of responsibility and perhaps unfair to some colleague, but if the patient is returned to you with the blessing of the consultant you will still have a satisfied and loyal patient. If we are to have patients who are loyal, we must have patients and their families who have faith in their doctors.

One of the most difficult and unhappy situations a doctor has to meet is when it becomes necessary for an oldster to be sent to a so-called convalescent hospital or nursing home. More often than not, this is the last trip but one; old people know it, fear it and hate it. It may seem like condemning them, and may create a hurt and terror that will make their remaining days miserable. But for the sake of other members of the family, for the sake of *their* health as well as the health and well-being of the patient, these situations must be faced. Hard decisions have to be made and for the sake of the doctor-patient relationship, again, it is often better to have the initial suggestion come from the family or a colleague. The attending physician should endorse the decision but let it seem to come from elsewhere.

A final word about office visits: Do not tell a patient to come back when they feel like it. Rather, show your interest and responsibility by telling the patient to come back at a specific time, whether it is in a week or a year. If you tell them you will send a bill if they fail to show up, it serves to emphasize your role as their doctor although it is but a minor joke.

In summary one has to remember that if called on to render services to geriatric patients, the greatest good and the greatest service will be achieved if the attending physician can retain the trust and confidence of the senior citizen and his or her family. Do not hold out false hope and in general be candid with the patient as much as possible—but do not close the door on hope. Always tell it to the family straight, but in the case of a very old or enfeebled patient it is not necessary "to hit them over the head" with the blunt truth. Remember there are yet quite a number of oldsters running around in a spritely manner who "have been given up by seven doctors and saved by Charlatan's Golden Tonic."

To close I would like to tell of a true happening in my practice about 50 years ago, in the Prohibition era. A rough, tough, portly sheriff, in his 60's, from a northern California county came to me for a checkup. He told me that he had recently been to one of the doctors in his home town who after a brief examination said "Sheriff, how many cigars have you been smoking?" "And I sez to Doc 'Now listen, Doc, old age has taken away one of my pleasures, national Prohibition has taken away another, and no dam' doctor is going to take away my one remaining pleasure!' "

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Health Hazard Appraisal Counseling—Continuing Evaluation

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A program of annual health examinations was expanded to include counseling based on a computerized appraisal of individual patients' specific health risk factors. Data obtained from a specially designed questionnaire, laboratory tests and a physical examination yielded a health hazard appraisal *showing a number of weighted risk factors and their relation to ten leading causes of death as determined for that patient. From all of this information, a "risk age" was developed which could then be compared with the patient's "true age." The results were reviewed with each patient, and methods of correcting health hazards were stressed. The first annual retesting of a group of 107 examinees showed a net risk age reduction of 1.4 years (formerly reported in this journal). The longer term follow-up reported in this paper showed a net risk reduction of 2.38 years in a group of 26 examinees. The net risk age reduction in the two groups represented 32 and 40 percent, respectively, of the achievable risk age reduction when patients comply with suggestions made during risk reduction counseling. These findings indicate that* health hazard appraisal *counseling is an effective method of altering priorities of health practices.*

MANY PROPONENTS of preventive medicine contend that the appraisal of health risk factors and the counseling of patients concerning those risks constitute an important part of health care.[1-5] The health hazard appraisal concept is based on the fact that each person faces certain health risks because of age, sex, race, heredity and lifestyle. When these factors are combined with information from a patient's medical history, physical examination, x-ray studies and laboratory tests, a physician is able to determine the health risk hazards of each patient. When the physician knows the prognostic characteristics of his patient and compares them with the experience of others having the same characteristics, he can quantitatively assess the health risks that the patient faces and counsel him accordingly. If the patient responds in an affirmative manner, his health risk factors can be reduced significantly.[6,7]

In health hazard appraisal, the degree of risk that an individual person faces is established from tables of mortality data on the United States population as a whole, by specific cause. These tables were developed by Harvey Geller of the United States Public Health Service.[8,9] For the health hazard appraisal, data from these tables are entered into a computer and combined with information on each patient's prognostic characteristics and medical condition. The combined data are then analyzed, and a computer printout

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TABLE 1.—*Ten-Year Mortality (Geller) Table for 45-Year-Old White Men*

Cause of Death	Chances in 100,000 of the Person Dying from This Cause		
	1960	1968	1974
Arteriosclerotic heart disease	3,507	3,539	2,973
Cancer of the lung	486	586	681
Cirrhosis	370	453	471
Vascular lesions of the central nervous system	428	385	299
Suicide	313	290	281
Motor vehicle accidents	313	360	260
Cancer of the large intestine and rectum	185	165	172
Pneumonia	185	193	113
Homicide	*	*	109
Bronchitis and emphysema	*	134	88
Other causes	3,473	2,875	2,158
Total causes of death	9,260	8,980	7,605

*Data not available.

is produced of the health hazard appraisal including a set of weighted factors that may positively or negatively alter the risk of death.

Factors of primary importance are blood pressure, presence of heart disease, overweight, smoking habits, use of alcohol and other aspects of lifestyle, as well as safety factors such as number of miles driven annually and use of seat belts. With the results of the computer printout, a physician can evaluate the outlook for his patient over the coming ten years, taking into account the "average" risk for the general population and the characteristics of his patient, which may alter the risk to be above or below the average.

Risk characteristics have been developed using data from the Framingham study,[10] the cigarette use and lung cancer study of Hammond and Horn,[11] and numerous studies conducted by the insurance industry, medical schools, hospitals and government agencies.[12,13] With this information, a risk factors manual has been developed to aid in health hazard appraisal.*

The Geller tables are critical input to the appraisal process. Table 1 shows the Geller data on an average 45-year-old white male American compiled for the years 1960, 1968 and 1974. According to these data, he has 7,605 chances in 100,000 of dying within the next ten years from heart disease, lung cancer, cerebrovascular accident, cirrhosis, suicide and a number of other causes. The following illustration shows how risk factors are applied to individual patients. A 45-year-old man smokes one package of cigarettes a day, but does not consume alcohol. His smoking, however, increases his ten-year risk of death to nearly 10,000 chances in 100,000. As a result, his risk becomes that of a 47-year-old man rather than his actual age of 45; he has a ten-year risk almost 2,000 chances in 100,000 greater than the average person of his age, race and sex who does not smoke. If he also used alcohol or smoked more than one package per day or both, his ten-year risk of death would increase greatly. If he were to stop smoking, however, he would reduce his risk by 26 percent, therefore giving him the risk factor of a 44-year-old man. With such quantitative information, the physician can counsel his patient on the benefits of affirmatively changing his lifestyle.

Four years ago, the NASA-Ames Research Center at Moffett Field, California, initiated a program of health hazard appraisal and counseling for its 1,600 employees, which was reported in 1975 in THE WESTERN JOURNAL OF MEDICINE.[14] The authors of the present paper reported the results of health hazard appraisal counseling of 488 employees of the National Aeronautics and Space Administration (NASA). Of those employees, 107 were randomly reappraised about a year later, with the finding that the net risk age among them was reduced by 1.4 years. This significant finding indicated that appraisal-based counseling is an effective method of altering priorities of health practices. The authors also evaluated patient acceptance of the health hazard appraisal. Their findings in this regard showed that 80 percent fully accepted the program and expressed the desire to be tested annually. Of the subjects, 50 percent interpreted their test results as indicating that they should change their health practices, and 80 percent indicated that they intended to make some or all of the recommended changes to lessen the risk of death in the next ten years.

The present paper assesses the results of later health hazard appraisals conducted in the NASA-Ames Research Center counseling program.

Methods

Most NASA-Ames employees participate in the program at the Ames Health Unit. Participants are given both a periodic health examination and a health hazard appraisal. The health examination includes x-ray study of the chest, spirometry, resting electrocardiography, submaximal stress electrocardiography, laboratory profiles, and a

*Available to physicians from the Methodist Hospital of Indiana, 1604 North Capital Avenue, Indianapolis, Indiana 46202, or as a computer-processed report from Interhealth, 2970 Fifth Avenue, San Diego, California 92103.

complete history and physical examination. The health hazard appraisal consists of a computer analysis of the answers to a six-page questionnaire concerning the patient's lifestyle, known diseases, family history, health habits, emotional status and racial background. Physical data are inserted into the questionnaire by the health unit personnel. To provide patient privacy, the questionnaires are identified only by the initials of the respondent and an identifying number.

Two weeks after the examination, the patient returns for health hazard appraisal counseling. A physician explains the results of the various tests and discusses any health risk factors that vary significantly from the population as a whole and thus constitute significant risks. In summarizing the data, the physician compares the patient's *true age* with his *risk age* as determined by the appraisal. The patient is then advised of the importance of changing his lifestyle and habits—for example, smoking, use of alcohol, or weight—and referred to his personal physician for any required treatment. The discussion focuses on the *achievable age,* the lowest possible risk age that the patient could achieve if, for example, he stopped smoking, modified his alcohol intake or reduced his weight. With lifestyle modification, the patient's risk age could become lower than his true age, and with total compliance, could reach his achievable age.

A sample health hazard appraisal printout is shown in Figure 1. The subject of this printout is a 40-year-old white man. For his age, race and sex the average risk of death in the next ten years is 5,490 chances in 100,000, based on the Geller tables. This patient's risk is considerably reduced, however, because of his favorable medical history and health practices. His present risk is 2,936 chances in 100,000 according to his health hazard appraisal, and his risk age is four years younger than his actual age. His risk factors include being slightly overweight, driving a motorcyle as an avocation and frequently not using seat belts when driving an automobile. If he complies with the recommendations shown in the right-hand column of the printout, his risk would be further reduced to 2,652 chances in 100,000, giving him a potential age of 33 years as compared with his actual age of 40 years. Information such as the foregoing was used to develop the Ames Health Unit program for patient counseling for risk reduction.

At the time of the present writing 1,225 Ames employees have participated in the physical examination/health hazard appraisal program. A group of 608 employees underwent a second examination/appraisal somewhat more than two years after the first. Slightly more than two years later, a small group (38) returned for a third examination/appraisal. The groups were not selected on any basis. They represent employees

AVERAGE	Risk/100,000	5,490	PRESENT AGE	40
PRESENT	Risk/100,000	2,936	RISK AGE	36
ACHIEVABLE	Risk/100,000	2,652	ACHIEVABLE AGE	33
CAUSE: Accidents, Motor Vehicles			AVERAGE RISK	339 (1.0)
			PRESENT RISK	305 (.9×Avg)
			ACHIEVABLE RISK	108 (.3×Avg)
		Present		
CONTRIBUTING FACTORS		*Risk*	ACHIEVABLE RISK WITH TREATMENT	
Alcohol: 1-2 drinks/week		1.0	None before driving	.5
Mileage—10,000 miles or more		.8		
Seat Belts: less than 10 percent usage ...		1.1	Always use seat belts	.8
CAUSE: Arteriosclerotic Heart Disease			AVERAGE RISK	1,861 (1.0)
			PRESENT RISK	130 (.1×Avg)
			ACHIEVABLE RISK	74 (.1×Avg)
		Present		
CONTRIBUTING FACTORS		*Risk*	ACHIEVABLE RISK WITH TREATMENT	
Exercise: some activity		1.0	Exercise as directed	.5
CAUSE: Cirrhosis of Liver			AVERAGE RISK	304 (1.0)
			PRESENT RISK	61 (.2×Avg)
			ACHIEVABLE RISK	30 (.1×Avg)
		Present		
CONTRIBUTING FACTORS		*Risk*	ACHIEVABLE RISK WITH TREATMENT	
Alcohol 1-2 drinks/week		.2	Stop drinking	.1

Figure 1.—Health hazard appraisal computer printout for a 40-year-old white man.

participating in the voluntary annual health examination program. Of this group, 26 have been studied to evaluate compliance with the health hazard appraisal counseling. Computer records of their former health hazard appraisals were located for comparative purposes to allow analysis of the same risk factors on all examinations. The remaining 12 patient records were not available for recomputation because of routine transfer of files.

Results

Statistics on the risk rate of the Ames personnel are presented in Table 2. The true death rate —that is, the likelihood of death per 100,000 in the upcoming ten years—has been calculated from national statistics based on age, race and sex. The risk death rate is based on those statistics as modified, positively or negatively, by the health hazard appraisal. The risk death rate reflects the employee's family history, health practices, and lifestyle. A significant reduction in the risk death rate occurred between the first and second evaluations. This reduction is evidenced by the 833 fewer chances of death per 100,000 shown in the table. The change between the second and third appraisals was even more substantial—with the risk of death reduced by 2,450 chances per 100,000.

TABLE 2.—*Average of Health Hazard Appraisal (HHA) Death Rate Results for the Ames Research Center Population (per 100,000)*

	True Death Rate	*Risk Death Rate*	*Difference (between true and risk death rates)*	*Risk Death Rate Reduction*
Initial HHA (N=1,225)	8,336	8,503	+ 167	..
Second HHA (N=608)	11,334	10,668	− 666	833
Third HHA. (N=26)	11,809	9,526	−2,283	2,450

The difference in subject age was 2.37 years between appraisals one and two and 1.1 years between appraisals two and three. It should be noted that time is a critical factor in such appraisals because the mortality curve steepens with each added year and, consequently, it becomes increasingly difficult to reduce the death risk (see Figure 2). The aging differential between the last two appraisals was only half as great as that between the first two. This factor probably explains the greater decrease in the death risk rate between

The risk of death is not constant. The graph below indicates the number of deaths per 100,000 population at various ages. Death rates go up very slowly until about age 30 and much more rapidly thereafter. Thus, a decrease in the death rate—say 650 deaths—as we get older represents the difference between the rate for people age 41 (point D) and that for people age 40 (point C). However, at the lower or younger end of the scale, a difference in deaths of that same number—650—represents the difference between people age 30 (point B) and those of age 14 (point A). Thus, when one is younger, his achievable age could go from 30 to 14 by reducing his risk of death by 650, whereas at age 41, a similar size risk reduction will have much less effect—only 1 year—reducing the age to 40.

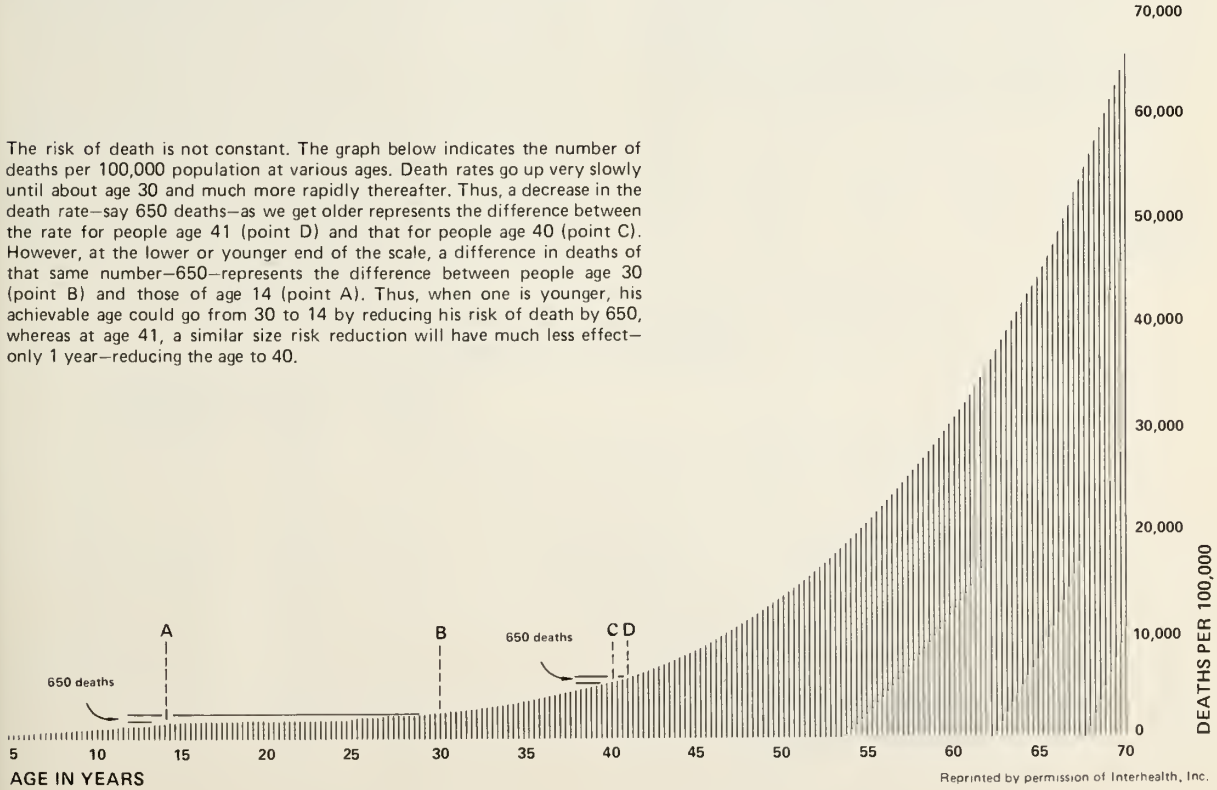

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Figure 2.—Mortality curve for the American population.

the second and third appraisals than that occurring between the first and second appraisals.

Shortly after the authors began to test this group, the health hazard appraisal computer programs were revised, having been updated on the basis of new research on risk factors prevalent in the American population. The data on the Ames group being studied at that time would not have been comparable unless the original appraisals were rerun using the new health hazard criteria. Unfortunately, the records of only 26 of the subjects were available for computer reevaluation with updated programs.

With the new data, the authors found that this group of employees had a reduction in risk age of 2.38 years as compared with the 1.4 years previously noted[16] (see Table 3). The findings, however, represent similar reductions of the difference between risk age and achievable age for the groups studied. A reduction in the first study of 1.4 years represented 32 percent of the achievable risk age reduction. In the current study, the reduction of 2.38 years represents 40 percent of the achievable risk age reduction.

The present study also sought to assess patient acceptance of the health hazard appraisal. A random sampling of patients—some participating in the program for the first time and others undergoing their second and third evaluations—were asked to complete a questionnaire to determine their impressions of this form of patient counseling. The responses indicated that most patients felt that their first appraisal provided them with significant information about their health (see Table 4). Over the four years of counseling the number who felt that they received important information declined slightly from 94 percent to 82 percent. On initial appraisal, 91 percent felt that they should change their lifestyles; after the third appraisal 87 percent still felt that way.

Patient confidence in the health hazard appraisal remained relatively stable over four years of the study although patients increasingly disagreed with the conclusions regarding their health. The authors observed that patients frequently became confused when new risk factors emerged in their appraisals after they had reduced earlier risk factors by changing their lifestyles. This reaction may account for the growing patient disagreement with appraisal recommendations. Table 1 shows the additional problem of the shift in numerical values of certain risk factors as the Geller tables are updated periodically. Some examinees find it unsettling to be presented with changes in risk factor counseling that are beyond their control.

The number of patients who intended to make changes in their lifestyles as a result of health hazard appraisal counseling declined from 94 percent on initial appraisal to 70 percent on the third appraisal. This degree of change may have resulted from the decreasing number of possible

TABLE 3.—*Average of Health Hazard Appraisal (HHA) Results on Third Periodic Examination (converted to age of employee in years)*

	True Age	*Risk Age*	*Achievable Age*	*Risk Age Reduction*
Initial HHA ..	48.04	47.96	43.92	...
Third HHA .. (N=26)	49.88	47.42	43.88	2.38

TABLE 4.—*Health Hazard Appraisal (HHA) Acceptance Obtained Through the Use of Questionnaire (percent)*

Question		*First HHA (N=33) (Percent)*	*Second HHA (N=45) (Percent)*	*Third HHA (N=23) (Percent)*
The results of the HHA showed me a	*great deal*	61	44	30
about the status of my health.	*moderate amount*	33	47	52
The results of the HHA showed me a	*great need*	0	13	9
for change in my lifestyle.	*moderate need*	55	56	39
	little need	36	24	39
I *agree* with the conclusions in the HHA results		91	78	65
disagree with some of the conclusions.		9	13	35
I *intend to* change my lifestyle accordingly.		24	20	22
make many changes		15	9	4
make some changes		55	56	44
I would like to take the HHA *every* year.		73	67	70
every other year		21	27	17

lifestyle changes available to the respondents as risk ages were reduced with subsequent health hazard appraisals. However, 70 percent expressed interest in continuing with annual counseling after the third health hazard appraisal. This interest offers promise that further reductions may be made in risk factors among the subject population as the program enters its fifth year.

Comments

Mortality statistics, at first glance, would appear to be unlikely data on which to base patient counseling concerning health practices. But these statistics provide the basis for a ten-year forecast of the death risk of individual patients and the substance for physicians to counsel their patients about improving their health habits. With the aid of mortality data and a health hazard appraisal, physicians can place various risk factors in an order of priority that patients can understand. Some factors that are included do not appear to be within the realm of the usual practice of medicine. But such factors as the use of seat belts and hazardous avocations can have an important bearing on the health hazard appraisal. And an important benefit of health hazard appraisal is that it concerns more than just the physiological aspects of a person's life.

As risk factors are further expanded and quantified, health hazard appraisal will become an increasingly important aspect of preventive medicine. With new data in new areas—such as personality typing and the impact of social changes on future health—the effectiveness of health hazard appraisal counseling will be enhanced.

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Refer to: Public Health Service recommendations for treatment of gonorrhea (Medical Information). West J Med 130: 286-289, Mar 1979

Medical Information

Public Health Service Recommendations for Treatment of Gonorrhea

Note: Physicians are cautioned to use no less than the recommended dosages of antibiotics.

Uncomplicated Gonococcal Infections in Men and Women

Drug Regimens of Choice

Aqueous procaine penicillin G (APPG) 4.8 million units injected intramuscularly at two sites, with 1 gram of probenecid by mouth.

or

Tetracycline hydrochloride* 0.5 gram by mouth four times a day for five days (total dosage 10 grams). Other tetracyclines are not more effective than tetracycline hydrochloride. All tetracyclines are ineffective as a single-dose therapy.

or

Ampicillin 3.5 grams, or amoxicillin 3 grams, either with 1 gram probenecid by mouth. Evidence shows that these regimens are slightly less effective than the other recommended regimens.

Patients who are allergic to the penicillins or probenecid should be treated with oral tetracycline as above. Patients who cannot tolerate tetracycline may be treated with spectinomycin hydrochloride 2 grams in one intramuscular injection.

Special Considerations

- Single-dose treatment is preferred in patients who are unlikely to complete the multiple-dose tetracycline regimen.
- The APPG regimen is preferred in men with anorectal infection.
- Pharyngeal infection is difficult to treat; high failure rates have been reported with ampicillin and spectinomycin.
- Tetracycline treatment results in fewer cases of postgonococcal urethritis in men.
- Tetracyline may eliminate coexisting chlamydial infections in men and women.
- Patients with incubating syphilis (seronegative, without clinical signs of syphilis) are likely to be cured by all above regimens except spectinomycin. All patients should have a serologic test for syphilis at the time of diagnosis.
- Patients with gonorrhea who also have syphilis or are established contacts to syphilis should be given additional treatment appropriate to the stage of syphilis.

Treatment of Sexual Partners

Men and women exposed to gonorrhea should be examined, cultured and treated at once with one of the regimens above.

Follow-up

Follow-up cultures should be obtained from the infected site, or sites, three to seven days after completion of treatment. Cultures should be obtained from the anal canal of all women who have been treated for gonorrhea.

Treatment Failures

A patient in whom therapy fails with penicillin, ampicillin, amoxicillin or tetracycline should be treated with 2 grams of spectinomycin intramuscularly.

Most recurrent infections after treatment with the recommended schedules are due to *reinfection* and indicate a need for improved contact tracing and patient education. Since infection by penicillinase (β-lactamase)-producing Neisseria gonorrhoeae is a cause of treatment failure, posttreatment isolates should be tested for penicillinase production.

Not Recommended

Although long-acting forms of penicillin (such as benzathine penicillin G) are effective in syphilo-

*Food and some dairy products interfere with absorption. Oral forms of tetracycline should be given one hour before or two hours after meals.

From the United States Department of Health, Education, and Welfare, Public Health Service, Center for Disease Control, Atlanta, GA 30333.

Submitted January 26, 1979.

These recommendations were established after deliberation with the following therapy consultants: Harold C. Neu, MD, College of Physicians and Surgeons, Columbia University; Erwin H. Braff, MD, San Francisco Department of Public Health; Gary Cunningham, MD, Southwestern Medical School, Dallas; King K. Holmes, MD, PhD, USPHS Hospital, Seattle; Franklyn Judson, MD, Department of Health and Hospitals, Denver; William McCormack, MD, State Laboratory Institute, Boston; Edwin M. Mears, Jr., MD, New England Medical Center, Boston; John D. Nelson, MD, Southwestern Medical School, Dallas; Morton Nelson, MD, Orange County, California; Suzanne M. Sgroi, MD, Suffield, Conn.; Frederick Sparling, MD, School of Medicine, The University of North Carolina, Chapel Hill; Lt Col Edmund C. Tramont, Walter Reed Army Medical Center, Washington, DC.

therapy, they have *no* place in the treatment of gonorrhea. Oral penicillin preparations such as penicillin V are not recommended for the treatment of gonococcal infection.

Penicillinase-Producing Neisseria Gonorrhoeae

Patients with uncomplicated pencillinase-producing Neisseria gonorrhoeae (PPNG) infections and their sexual contacts should receive spectinomycin 2 grams intramuscularly in a single injection. Because gonococci are very rarely resistant to spectinomycin and reinfection is the most common cause of treatment failure, patients with positive cultures after spectinomycin therapy should be retreated with the same dose.

A PPNG isolate that is resistant to spectinomycin may be treated with cefoxitin 2 grams in a single intramuscular injection, with probenecid 1 gram by mouth.

Treatment in Pregnancy

All pregnant women should have endocervical cultures for gonococci as an integral part of the prenatal care at the time of the first visit. A second culture late in the third trimester should be obtained from women at high risk for gonococcal infection.

Drug regimens of choice are APPG, ampicillin or amoxicillin, each with probenecid as described above.

Women who are allergic to penicillin or probenecid should be treated with spectinomycin.

Refer to the sections on acute salpingitis and disseminated gonococcal infections for the treatment of these conditions during pregnancy. Tetracycline should not be used in pregnant women because of potential toxic effects for mother and fetus.

Acute Salpingitis (Pelvic Inflammatory Disease)

There are no reliable clinical criteria on which to distinguish gonococcal from nongonococcal salpingitis. Endocervical cultures for N. gonorrhoeae are essential. Therapy should be initiated immediately.

Admission to hospital should be strongly considered in the following situations:

- Uncertain diagnosis, in which surgical emergencies such as appendicitis and ectopic pregnancy must be excluded.
- Suspicion of pelvic abscess.
- Severely ill patients.
- Pregnancy.
- Inability of the patient to follow or tolerate an outpatient regimen.
- Failure to respond to outpatient therapy.

Antimicrobial Agents

Outpatient treatment

Tetracycline* 0.5 gram taken orally four times a day for ten days. This regimen should not be used for pregnant patients.

or

APPG 4.8 million units intramuscularly, ampicillin 3.5 grams or amoxicillin 3 grams each with probenecid 1 gram. Either regimen is followed by ampicillin 0.5 gram or amoxicillin 0.5 gram orally four times a day for ten days.

Patients in hospital

Aqueous crystalline penicillin G 20 million units given intravenously each day until improvement occurs, followed by ampicillin 0.5 gram orally four times a day to complete ten days of therapy.

or

Tetracycline* 0.25 gram given intravenously four times a day until improvement occurs, followed by 0.5 gram orally four times a day to complete ten days of therapy. This regimen should not be used for pregnant women. The dosage may have to be adjusted if renal function is depressed.

Since optimal therapy for patients in hospital has not been established, other antibiotics in addition to penicillin are frequently used.

Special Considerations

- Failure of the patient to improve on the recommended regimens does not indicate the need for stepwise additional antibiotics but requires clinical reassessment.
- Intrauterine devices are risk factors for the development of pelvic inflammatory disease. The effect of removing an intrauterine device on the response of acute salpingitis to antimicrobial therapy and on the risk of recurrent salpingitis is unknown.
- Adequate treatment of women with acute salpingitis must include examination and appropriate treatment of their sex partners because of

*Food and some dairy products interfere with absorption. Oral forms of tetracycline should be given one hour before or two hours after meals.

the high prevalence of nonsymptomatic urethral infection. Failure to treat sex partners is a major cause of recurrent gonococcal salpingitis.

- Follow-up of patients with acute salpingitis is essential during and after treatment. In all patients repeat cultures should be done for N. gonorrhoeae after treatment.

Acute Epididymitis

Acute epididymitis can be caused by N. gonorrhoeae, Chlamydia or other organisms. If gonococci are shown by Gram stain or culture of urethral secretions, treatment should be as follows:

APPG 4.8 million units, ampicillin 3.5 grams or amoxicillin 3 grams, each with probenecid 1 gram. Either regimen is followed by ampicillin 0.5 gram or amoxicillin 0.5 gram orally four times a day for ten days.

or

Tetracyline* 0.5 gram orally four times a day for ten days.

If gonococci are not shown to be present, the above tetracycline regimen should be used.

Disseminated Gonococcal Infection

Arthritis-Dermatitis Syndrome

Equally effective treatment schedules in the arthritis-dermatitis syndrome include the following:

Ampicillin 3.5 grams or amoxicillin 3 grams orally, each with probenecid 1 gram, followed by ampicillin 0.5 gram or amoxicillin 0.5 gram four times a day orally for seven days.

or

Tetracycline* 0.5 gram orally four times a day for seven days. Tetracycline should not be used for complicated gonococcal infection in pregnant women.

or

Spectinomycin 2 grams intramuscularly twice a day for three days (treatment of choice for disseminated infections caused by PPNG).

or

Erythromycin 0.5 gram orally four times a day for seven days.

or

Aqueous crystalline penicillin G 10 million units intravenously per day until improvement occurs, followed by ampicillin 0.5 gram four times a day to complete seven days of antibiotic treatment.

Special Considerations

- Admission to hospital is indicated for patients who may be unreliable, have uncertain diagnosis, or have purulent joint effusions or other complications.
- Open drainage of joints other than the hip is not indicated.
- Intraarticular injection of antibiotics is unnecessary.

Gonococcal Meningitis and Endocarditis

Meningitis and endocarditis caused by the gonococcus require high-dose intravenous penicillin therapy. In penicillin-allergic patients with endocarditis, desensitization and administration of penicillin is indicated; chloramphenicol may be used in penicillin-allergic patients with meningitis.

Gonococcal Infections in Pediatric Patients

With gonococcal infections in children beyond the newborn period the possibility of sexual abuse must be considered. Genital, anal and pharyngeal cultures should be obtained from all patients before antibiotic treatment. Appropriate cultures should be obtained from persons who have had contact with the child.

Prevention of Gonococcal Ophthalmia

When required by state legislation or indicated by local epidemiologic considerations, effective and acceptable regimens for prophylaxis of neonatal gonococcal ophthalmia include the following:

Ophthalmic ointment or drops containing tetracycline or erythromycin.

or

One percent silver nitrate solution.

Special Considerations

- Bacitracin is not recommended.
- The value of irrigation after application of silver nitrate is unknown.

Management of Infants Born to Mothers With Gonococcal Infection

Infants born to mothers with gonorrhea are at high risk of infection and require treatment with a single intravenous or intramuscular injection of aqueous crystalline penicillin G 50,000 units to full-term infants or 20,000 units to low-birth-

*Food and some dairy products interfere with absorption. Oral forms of tetracycline should be given one hour before or two hours after meals.

weight infants. Topical prophylaxis for neonatal ophthalmia is not adequate treatment. Clinical illness requires additional treatment.

Neonatal Disease

Gonococcal Ophthalmia

Patients should be admitted to hospital and isolated for 24 hours after initiation of treatment. Untreated gonococcal ophthalmia is highly contagious. Aqueous crystalline penicillin G 50,000 units per kg of body weight per day in two doses intravenously should be administered for seven days. Saline irrigation of the eyes should be done as needed. Topical antibiotic preparations alone are not sufficient or required when appropriate systemic antibiotic therapy is given.

Complicated Infection

Patients with arthritis and septicemia should be admitted to hospital and treated with aqueous crystalline penicillin G 75,000 to 100,000 units per kg of body weight per day intravenously in two or three divided doses for seven days. Meningitis should be treated with aqueous crystalline penicillin G 100,000 units per kg of body weight per day, divided into three or four intravenous doses, and continued for at least ten days.

Childhood Disease

Children who weigh 45 kg (100 pounds) or more should receive adult regimens. Children who weigh less than 45 kg should be treated as follows:

Uncomplicated Disease

Uncomplicated vulvovaginitis, urethritis, proctitis or pharyngitis can be treated at one visit with:

Amoxicillin 50 mg per kg of body weight orally with probenecid 25 mg per kg (maximum 1 gram).

or

Aqueous procaine penicillin G 100,000 units per kg intramuscularly plus probenecid 25 mg per kg (maximum 1 gram).

Special Considerations

- Topical or systemic estrogen therapy (or both) is of no benefit in vulvovaginitis.
- Long-acting penicillins, such as benzathine penicillin G, are not effective.
- All patients should have follow-up cultures and the source of infection should be identified, examined and treated.

Gonococcal Ophthalmia

Ophthalmia in children is treated as in neonates but the dose of penicillin is increased to 100,000 units per kg of body weight per day, given intravenously.

Complicated Infections

Patients with peritonitis or arthritis require admission to hospital and treatment with aqueous crystalline penicillin G, 100,000 units per kg of body weight per day intravenously for seven days. Aqueous crystalline penicillin G 250,000 units per kg per day given intravenously in six divided doses for at least ten days is recommended for meningitis.

Allergy to Penicillins

Children who are allergic to penicillins should be treated with spectinomycin 40 mg per kg of body weight, given intramuscularly. Children older than 8 years may be treated with tetracycline 40 mg per kg per day given orally in four divided doses for five days. For treatment of complicated disease, the alternative regimens recommended for adults may be used in appropriate pediatric dosages.

ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles that they consider to be important in other journals. The editors believe that these titles together with a brief assessment of the articles are worth publishing for the information of our readers.*

In Defense of the Pill

Goldziehr JW

Journal of Continuing Education in Obstetrics and Gynecology
Oct 1978, pp 15-32

DISCIPLINES: Obstetrics, Gynecology, General and Family Practice

READABILITY: Very good

In this scholarly review of a most controversial subject, "The Pill—good or bad?", an eminent and respected gynecologist bursts the bubble of misinformation blown up by the lay press. The many anecdotal, prospective and retrospective studies are carefully analyzed. Sensible advice for anyone prescribing or using the Pill.

Technologic Intervention in Obstetrics: Has the Pendulum Swung Too Far?

Baker RA

Obstetrics and Gynecology
51:241-243, Feb 1978

DISCIPLINES: Obstetrics, Family Practice

READABILITY: Excellent

A timely analysis of the present trends in the use of amniocentesis, fetoscopy, fetal monitoring and cesarean section. The author pleads with his fellow obstetricians to "intervene with technologic tools only when such action is supported by sound clinical judgment."

Vacuum Extraction—Use in a Community Hospital Setting

Plauche WC

Obstetrics and Gynecology
52:289-293, Sep 1978

DISCIPLINES: General and Family Practice, Obstetrics, Gynecology

READABILITY: Excellent

The author's enthusiam for the vacuum extractor is tempered by the incidence (18.7 percent) of "significant trauma to the fetal scalp." He believes that vacuum extraction requires careful choices of cases and indications. When these are satisfied, vacuum extraction can solve some perplexing obstetrical problems.

Perioperative Antibiotic Prophylaxis in Cesarean Section

Kreutner AK, Del Bene VE, Delamar D, et al

Obstetrics and Gynecology
52:279-284, Sep 1978

DISCIPLINES: General and Family Practice, Obstetrics, Gynecology, Surgery

READABILITY: Good

"Shall we or shall we not use perioperative antibiotic prophylaxis in cesarean section?" The authors conclude that a short course of cephalosporin given perioperatively to cesarean section patients does not reduce the number of resistant Gram-negative bacilli in the genital tract or significantly reduce morbidity.

Replacement Estrogen Therapy for Menopausal Vasomotor Flushes—Comparison of Quinestrol and Conjugated Estrogens

Baumgardner SB, Cordrea H, Daane TH, et al

Obstetrics and Gynecology
51:445-451, Apr 1978

DISCIPLINES: General Practice, Gynecology, Obstetrics

READABILITY: Very good

In a double-blind, placebo-controlled trial, a "new" estrogen, quinestrol (Estrovis®, Warner-Chilcott) was judged as effective as conjugated estrogen (Premarin®) in controlling vasomotor flushes. Possible advantages are once-a-week dosage, and possibly fewer side effects.

Evaluation of a Dipstick for Candida

Weissberg SM

Obstetrics and Gynecology
52:506-509, Oct 1978

DISCIPLINES: Obstetrics, Gynecology, General and Family Practice

READABILITY: Very good

"Doctor, I think I have an infection!" For this woman, and her physician, a new dipstick test for Candida vaginal infection could be a most welcome adjunct to diagnosis and treatment. Now commercially available, it is praised as being simple, quick, economical, accurate and adapted to office use.

—E. R. W. FOX, MD
Coeur d'Alene, ID

in memoriam

ALSTON, EDWIN F., San Francisco. Died December 9, 1978 in San Francisco of cancer, aged 59. Graduate of Harvard Medical School, Boston, 1944. Licensed in California in 1947. Dr. Alston was a member of the San Francisco Medical Society.

ANDERSON, THOMAS W., Santa Ana. Died November 29, 1978 in Santa Ana, aged 57. Graduate of the University of Chicago, The School of Medicine, 1945. Licensed in California in 1949. Dr. Anderson was a member of the Orange County Medical Association.

BINKLEY, THOLOW, Sacramento. Died January 4, 1979, aged 91. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1923. Licensed in California in 1923. Dr. Binkley was a retired member of the Sacramento County Medical Society.

CARLSON, SAMUEL S., Vallejo. Died November 13, 1978 in Vallejo, aged 79. Graduate of Long Island College of Medicine, New York City, 1925. Licensed in California in 1937. Dr. Carlson was a member of the Solano County Medical Society.

CARMODY, WILMA G., El Cajon. Died June 4, 1978, aged 86. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1948. Licensed in California in 1949. MD degree from California College of Medicine, 1962. Dr. Carmody was a retired member of the San Diego County Medical Society.

CROWE, HAROLD E., Los Angeles. Died January 7, 1979 in Los Angeles of injuries received in traffic accident, aged 83. Graduate of Université Libre de Bruxelles Faculté de Médecine, 1922. Licensed in California in 1926. Dr. Crowe was a member of the Los Angeles County Medical Association.

CROWL, VERNE S., Laguna Hills. Died June 2, 1978, aged 87. Graduate of the University of Minnesota Medical School, Minneapolis, 1920. Licensed in California in 1924. Dr. Crowl was a member of the Los Angeles County Medical Association.

DOCKWEILER, JOHN ELDREDGE STEARNS, Los Angeles. Died November 8, 1978 in Los Angeles, age 52. Graduate of Cornell University Medical College, New York, 1950. Licensed in California in 1951. Dr. Dockweiler was a member of the Los Angeles County Medical Association.

FLYNN, GEORGE THOMAS, Santa Barbara. Died November 12, 1978 in Santa Barbara of cancer, aged 65. Graduate of St. Louis University School of Medicine, 1939. Licensed in California in 1948. Dr. Flynn was a member of the Medical Society of Santa Barbara County.

FRYE, JOHN WILLIAM, Fresno. Died November 16, 1978 in Fresno of lung cancer, aged 57. Graduate of the University of Wisconsin Medical School, Madison, 1946. Licensed in California in 1955. Dr. Frye was a member of the Fresno-Madera Medical Society.

GABLE, TOM P., SR., San Diego. Died January 8, 1979 in his San Diego home of injuries suffered in an accidental fall, aged 59. Graduate of the University of Oklahoma School of Medicine, Oklahoma City, 1943. Licensed in California in 1944. Dr. Gable was a member of the San Diego County Medical Society.

GAN, ALLEN, El Sobrante. Died May 29, 1978, aged 47. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1956. Licensed in California in 1957. Dr. Gan was a member of the Alameda-Contra Costa Medical Association.

GINDES, BERNARD C., Los Angeles. Died June 2, 1978 of cardiorespiratory arrest, aged 59. Graduate of National Autonomous University School of Medicine, Mexico City, 1956. Licensed in California in 1959. Dr. Gindes was a member of the Los Angeles County Medical Association.

GREEN, BERTRAM J., Santa Rosa. Died December 27, 1978 in Santa Rosa of Parkinson disease and heart disease, aged 71. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1934. Licensed in California in 1934. MD degree from California College of Medicine, 1962. Dr. Green was a retired member of the Sonoma County Medical Association.

HARVEY, CARL GEORGE, Healdsburg. Died November 29, 1978 in Santa Rosa of heart disease, aged 58. Graduate of the University of Pittsburgh School of Medicine, 1951. Licensed in California in 1954. Dr. Harvey was a member of the Sonoma County Medical Association.

HINSHAW, ROBERT PATTON, Beverly Hills. Died November 15, 1978, aged 60. Graduate of the University of Southern California School of Medicine, Los Angeles, 1952. Licensed in California in 1952. Dr. Hinshaw was a member of the Los Angeles County Medical Association.

LAMON, J. DANIEL, JR., San Jose. Died January 15, 1979 in San Jose, aged 77. Graduate of the Medical College of Georgia, Augusta, 1925. Licensed in California in 1946. Dr. Lamon was a retired member of the Santa Clara County Medical Society.

LEAKE, WILLIAM H., Santa Monica. Died December 6, 1978 in Santa Monica of cancer, aged 84. Graduate of Vanderbilt University School of Medicine, Nashville, 1916. Licensed in California in 1922. Dr. Leake was a member of the Los Angeles County Medical Association.

LION, ERNEST G., San Francisco. Died January 3, 1979 in Sausalito, aged 74. Graduate of Syracuse University College of Medicine, 1933. Licensed in California in 1934. Dr. Lion was a member of the San Francisco Medical Society.

LOWE, STEPHEN SPENCER, Santa Rosa. Died December 10, 1978 in Santa Rosa, aged 42. Graduate of the University of Nebraska College of Medicine, Omaha, 1961. Licensed in California in 1968. Dr. Lowe was a member of the Sonoma County Medical Association.

MANER, GEORGE D., Los Angeles. Died December 24, 1978 of carcinoma of the stomach with metastases, aged 80. Graduate of the Medical College of Georgia, Augusta, 1919. Licensed in California in 1920. Dr. Maner was a member of the Los Angeles County Medical Association.

MCSPARRAN, JOSEPH L., San Diego. Died December 27, 1978 in San Diego, aged 94. Graduate of the University College of Medicine, Richmond, Virginia, 1912. Licensed in California in 1942. Dr. McSparran was a retired member of the San Diego County Medical Society.

PURDY, ANN PERIL, San Francisco. Died December 10, 1978 of cerebrovascular accident, aged 90. Graduate of Johns Hopkins University School of Medicine, Baltimore, 1919. Licensed in California in 1931. Dr. Purdy was a member of the San Francisco Medical Society.

RIEGER, THEODORE A., Pasadena. Died June 12, 1978 of malignant melanoma, aged 83. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1929. Licensed in California in 1929. MD degree from California College of Medicine, 1962. Dr. Rieger was a member of the Los Angeles County Medical Association.

ROMBEAU, LEE PAYNE, La Jolla. Died April 18, 1978 of coronary occlusion, aged 69. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1935. Licensed in California in 1935. Dr. Rombeau was a retired member of the Los Angeles County Medical Association.

SCHLOSBERG, STANLEY S., Los Angeles. Died November 11, 1978, aged 64. Graduate of Dalhousie University Faculty of Medicine, Halifax, 1939. Licensed in California in 1947. Dr. Schlosberg was a member of the Los Angeles County Medical Association.

SEILER, WILLIAM E., Pacific Beach. Died November 17, 1978 in Pacific Beach, aged 69. Graduate of the Creighton University School of Medicine, Omaha, 1936. Licensed in California in 1937. Dr. Seiler was a member of the San Diego County Medical Society.

SHERMAN, ALLEN H., San Francisco. Died December 12, 1978 in San Francisco, aged 65. Graduate of the University of California Medical School, Berkeley-San Francisco, 1939. Licensed in California in 1939. Dr. Sherman was a member of the San Francisco Medical Society.

SWENGEL, WINTON FRANKLIN, Monterey. Died October 13, 1978 in Monterey, aged 70. Graduate of Rush Medical College, Chicago, 1933. Licensed in California in 1933. Dr. Swengel was a member of the Monterey County Medical Society.

TAYLOR, JOHN H., Burlingame. Died November 13, 1978 in Palo Alto of leukemia, aged 42. Graduate of the Creighton University School of Medicine, Omaha, 1961. Licensed in California in 1962. Dr. Taylor was a member of the San Mateo County Medical Society.

WAKEFIELD, WILLIAM, Albany. Died December 10, 1978 in Mexico, aged 72. Graduate of McGill University Faculty of Medicine, Montreal, 1935. Licensed in California in 1951. Dr. Wakefield was a retired member of the Alameda-Contra Costa Medical Association.

WATSON, ROBERT L., JR., Los Angeles. Died January 22, 1979 in Los Angeles, aged 56. Graduate of the University of Southern California School of Medicine, Los Angeles, 1947. Licensed in California in 1947. Dr. Watson was a member of the Los Angeles County Medical Association.

WILLIAMS, FLETA H., San Jose. Died November 27, 1978 in San Jose of heart disease, aged 88. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1929. Licensed in California in 1939. Dr. Williams was a retired member of the Santa Clara County Medical Society.

WONG, THOMAS A., Los Angeles. Died January 2, 1979, aged 71. Graduate of the University of California Medical School, Berkeley-San Francisco, 1933. Licensed in California in 1933. Dr. Wong was a member of the Los Angeles County Medical Association.

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WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

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DIRECTOR, FAMILY PRACTICE PROGRAM. Opportunity to implement own ideas in teaching and administration. Program is part of the University of California, Davis, Family Practice Network. Faculty appointment, competitive salary and benefits; Board Certification by ABFP required. Practice and teaching experience desirable. Send curriculum vitae to: L. Thomas Fife, MD, Associate Director, Family Practice Residency Program, Merced Community Medical Center, PO. Box 231, Merced, CA 95340.

(Continued on Page 22)

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Challenging new occupational and environmental medicine residency/fellowship program funded by a NIOSH Educational Resource Center has begun at the University of Utah. Two-year program leads to Master of Science in Community Medicine (M.P.H. equivalent), a research thesis, clinical training and preceptorships with industry and labor. Combined programs with family practice (4 years) and in pulmonary disease for internists (3 years) available. First year clinical training can be provided. Contact: **William N. Rom, MD, MPH, Director, RMCO-EH, Room BC106, University of Utah Medical Center, Salt Lake City, Utah 84132.** The University of Utah is an Equal Opportunity Employer.

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OPHTHALMOLOGIST needed for group in LA County. Complete lab and x-ray facilities. Starting salary is $5,000 per month with increments to follow. Free health and accident insurance, mal-practice and medical dues paid. Contact Madeline Borquez, 2675 E. Slauson, Huntington Park, CA 90255. Phone (213) 589-6681.

PEDIATRICIAN needed for group in LA County. Complete x-ray and lab facilities. Salary is $5,000 per month w/increments to follow. Free health and accident insurance, mal-practice and medical dues paid. Contact Madeline Borquez, 2675 E. Slauson Ave., Huntington Park, CA 90255. Phone (213) 589-6681.

GP needed for large group in LA County. Complete x-ray and lab facilities. Starting salary is $5,000 per month w/increments to follow. Free health and accident insurance, mal-practice and medical dues paid. Contact Madeline Borquez, 2675 E. Slauson Ave., Huntington Park, CA 90255. Phone (213) 589-6681.

OB/GYN needed for large group in LA County. Complete x-ray and lab facilities. Starting salary is $5,000 per month w/increments to follow. Free health and accident insurance, mal-practice and medical dues paid. Contact Madeline Borquez, 2675 E. Slauson Ave., Huntington Park, CA 90255. Phone (213) 589-6681.

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(Continued from Page 23)

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GENERAL SURGEON, 35, board certified. Preferably group with academic-ties in metropolitan area. Interest in geriatric surgery. Experience in endoscopy. Reply Box 6029, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PEDIATRICIAN—32, board certified, California license. Wishes to join a group practice in Bay area. Excellent training and experience, personable. Write Box 6028, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST WITH SUBSPECIALTY, 33, FMG, wife also MD, will buy practice or situation with guaranteed salary—in California. Available immediately, no agents. Please write Box 6031, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PHYSICIAN with 10 years experience in preventive and occupational medicine and postgraduate training for 4 years, seeks position in San Francisco/Bay Area in medical outpatient clinic. Write Box 6020, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

RADIOLOGIST—41, Board Certified. California license. Desire California, Oregon or Arizona location. Experience in CT, Ultrasound, Nuclear Medicine and Angiography. UCSF fellowship and academic and private practice experience. Administrative experience prior to medical training. Write Box 6033, Western Journal of Medicine, 731 Market Street, San Francisco, CA 94103.

ABIM, age 33, finishing infectious disease fellowship summer 1979. Seeks group or hospital based practice, would welcome association with microbiology laboratory and/or house staff program. Write Box 6032, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

LOCUM TENENS WORK WANTED

LOCUM TENENS in general practice office, San Francisco Bay Area for August 1979 and possibly September 1979 Salary/percentage. Write Box 6026, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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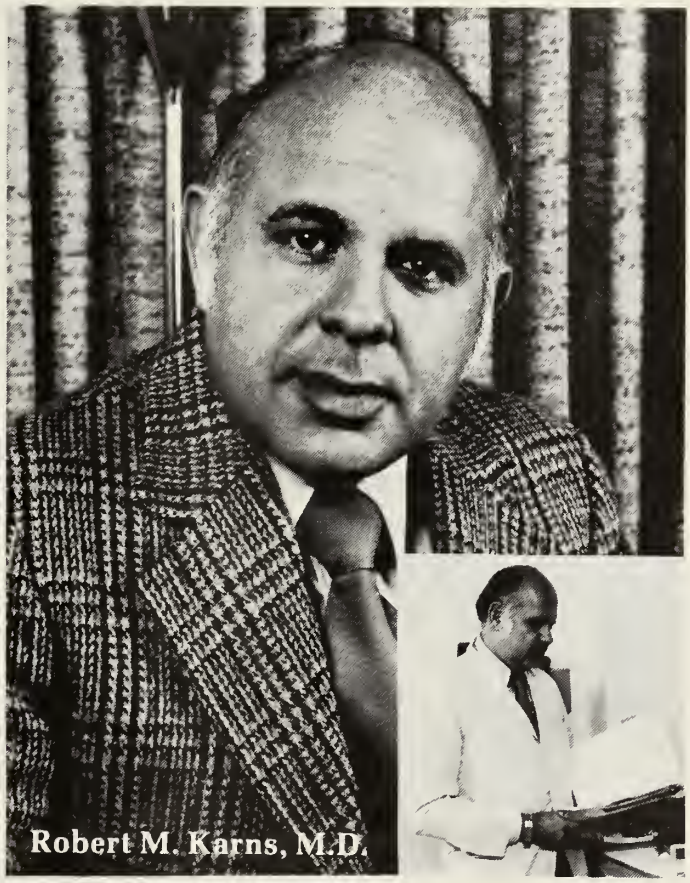

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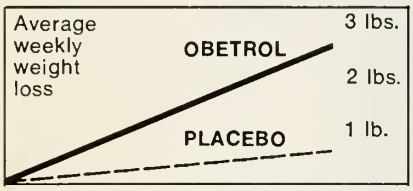

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Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

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3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

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ANESTHESIOLOGY

March 18-23—**Anesthesiology 1979—5th Annual Winter Meeting.** Anesthesiology Educational Foundation and CSA at Mammoth Lakes. Sunday-Friday. Contact: Ronald L. Katz, MD, AEF, 3377 Colbert St., Los Angeles 90066.

April 20-22—**Newer Concepts and Older Practices in Obstetrical Anesthesia.** Fresno Community Hospital. Friday-Sunday. Contact: Joanne Ellis, Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

April 30-May 4—**California Society of Anesthesiologists—Hawaii Seminar.** Kauai Surf Hotel, Kauai. Monday-Friday. 20 hrs. Contact: CSA, Inc., 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

May 6-12—**16th Biennial Western Conference on Anesthesiology.** Sheraton Waikiki, Honolulu. One week. Contact: BWCA, 707-2525 Willow St., Vancouver, B.C., Canada V5Z 3N8.

May 31-June 4—**California Society of Anesthesiologists—Annual Scientific Meeting.** Disneyland Hotel, Anaheim. Thursday-Monday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

CANCER

March 16—**Annual Cancer Symposium.** California Hospital Medical Center, Los Angeles. Friday. Contact: Kenneth L. Senter, MD, Dir., Med. Ed., CHMC, 1414 S. Hope St., Los Angeles 90015. (213) 748-2411, ext. 251.

March 17—**Cancer Viewpoints No. 8—Thyroid Cancer Diagnosis and Treatment.** American Cancer Society, Contra Costa Unit, at John Muir Hospital, Walnut Creek. Saturday. Contact: ACS, Contra Costa Unit, 1341 Newell Ave., Walnut Creek 94596. (415) 934-7640.

March 23-24—**Body Image, Self-Esteem and Sexuality in Cancer Patients—14th Annual San Francisco Cancer Symposium.** West Coast Cancer Foundation and St. Mary's Hospital and Medical Center at Hyatt on Union Square, San Francisco. Friday-Saturday. $100 before Dec. 1; $125 after. Contact: Jerome M. Vaeth, MD, WCCF, 50 Francisco St., Suite 200, San Francisco 94133. (415) 981-4590.

April 4-6—**American Cancer Society National Conference—Urologic Cancer 1979.** Hilton Hotel, Los Angeles. Wednesday-Friday. 15½ hrs. Contact: Urologic Cancer Conference. 777 Third Ave., New York 10017. (212) 371-2900, ext. 239.

April 7—**San Joaquin County American Cancer Society Conference—2nd Annual.** ACS, San Joaquin-Calaveras Unit, and San Joaquin Hospital at San Joaquin Delta College, Stockton. Saturday. 7 hrs. $25. Contact: ACS, San Joaquin-Calaveras Unit, 1111 W. Robinhood Dr., Stockton 95207.

May 12—**Genital Urinary Cancer.** San Francisco Regional Cancer Foundation at Fireman's Fund Building, San Francisco. Saturday. 4 hrs. Contact: Norma Schlager, PhD, S.F. Regional Cancer Fnd., 14th and Lake, San Francisco 94118. (415) 221-2132.

July 13-14—**Oncology Symposium.** Area Health Education Center, UCSF, at Del Monte Hyatt, Monterey. Friday-Saturday. Contact: Remi Barron, Area Health Education Ctr., P.O. Box 1611, Salinas 93902. (408) 757-3616.

EMERGENCY MEDICINE

March 19-23—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at Bahia Hotel, San Diego. Monday-Friday. 40 hrs. $350.

March 22—**Venous Animal Injuries.** General Hospital Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at Gen. Hosp., Ventura. Thursday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

March 26-29—**American College of Emergency Physicians—Annual Symposium.** Del Monte Hyatt, Monterey. Monday-Thursday. 16 hrs. $235, members; $265, nonmembers. Contact: Registrar, ACEP, 3900 Capital City Blvd., Lansing, MI 48906. (517) 321-7913.

April 2-6—**Medical Management of EMS Systems.** UCSD at Hilton, San Diego. Monday-Friday. 36 hrs. $120.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

April 21-28—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 29 hrs. $325.

April 30—**Polyneuropathies.** General Hospital Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at General Hospital, Ventura. Monday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

May 7-11—**Topics in Emergency Medicine.** UCSF at Sheraton, Fisherman's Wharf, San Francisco. Monday-Friday.

May 14-18—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Islandia Hyatt House, San Diego. Monday-Friday. 40 hrs. $350.

May 19—**Emergency Radiology.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7½ hrs. $50.

May 21—**Hand Injuries.** General Hospital Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at General Hospital, Ventura. Monday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

May 26-June 2—**Annual Symposium on Diagnosis and Management of Medical Emergencies.** West Hills Hospital at Royal Lahaina Hotel, Maui, Hawaii. One week. 30 hrs. Contact: Charlotte McGuire, Adm. Coordinator, Medical Staff, West Hills Hosp., 7300 Medical Center Dr., Canoga Park 91307. (213) 884-7060, ext. 200.

June 25-29—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

August 13-17—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 43 hrs. $350.

MEDICINE

March 17—**Clinical Aspects of Hypertension.** STAN. Saturday. 5 hrs. $30.

March 23-25—**Cardiac Symptoms, Arrhythmias and Holter Monitoring.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

March 24—**The Abdomen and G.I. Tract—Update 1979.** Memorial Hospital Medical Center of Long Beach—UCI Center for Health Education and V.A. Hospital of Long Beach. Saturday. 7 hrs. Contact: Edward I. Greenbaum, MD, V.A. Hosp., 5901 E. 7th St., Long Beach 90822. (213) 498-6264.

March 26-28—**Occupational Skin Diseases.** UCSF at Golden Gateway Holiday Inn, San Francisco. Monday-Wednesday.

March 26-29—**American College of Physicians—60th Annual Session.** San Francisco. Monday-Thursday. Contact: ACP, 4200 Pine St., Philadelphia, PA 19104.

March 26-April 6—**Intensive Review of Internal Medicine.** USC. Two weeks. 69 hrs. $325.

March 29-30—**International Symposium on the Larynx.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Friday.

March 29-30—**Cardiovascular Nuclear Medicine—Current Concepts and Their Clinical Applications.** Foundation for Cardiovascular Research and Peralta Hospital at Stanford Court Hotel, San Francisco. Thursday-Friday. 12 hrs. Contact: FCR, 201 N. El Molino, Suite 100, Pasadena 91101.

March 29-31—**Contemporary Management of Acute Myocardial Infarction by the Family Physician.** American College of Cardiology and American Academy of Family Physicians at Riviera Hotel, Palm Springs. Thursday-Saturday. Contact: Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

March 31—**Flexible Fiberoptic Bronchoscopy.** PMC. Saturday. 6 hrs. $325.

March 31-April 1—**Important Liver Disease: Its Diagnosis, Pathophysiology and Management.** American Liver Foundation and Desert Hospital at Desert Hospital, Palm Springs. Saturday-Sunday. 9 hrs. $110; $55, residents and fellows. Contact: William E. Rush, MD, Desert Hosp., P.O. Box 1627, Palm Springs 92262. (714) 323-6141.

April 2-11—**Cardiology for the Consultant: A Clinician's Retreat.** American College of Cardiology at Rancho Santa Fe. 10 days. Contact: Mary Anne McInerny, Dir., Extramural Programs Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

April 3-5—**American Laryngological, Rhinological and Otological Society—Annual Meeting.** See Surgery, April 3-5.

April 4—**Antimicrobial Therapy: The State of the Art.** L.A. Society of Internal Medicine. Wednesday. 1 hr. Contact: Susan McNamara, LASIM, 8530 Wilshire Blvd., No. 313, Beverly Hills 90211. (213) 659-6750.

April 4-June 13—**Rheumatology for the Practicing Physician.** UCLA at Wadsworth VA Hospital Center, Los Angeles. Wednesday evenings. 20 hrs. $220.

April 11-13—**Review and Updating of the Immunology and Clinical Practice of Allergy—3rd Annual.** UCSD at Hilton Hotel, San Diego. Wednesday-Friday.

April 18—**Thyroid '79.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. $50. Contact: Janie Sternal, CME Coordinator, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

April 18—**Society of Nuclear Medicine, Southern California Chapter.** See Radiology and Pathology, April 18.

April 26-June 14—**Current Practical Cardiology—1979.** Daniel Freeman Hospital, Inglewood. Thursdays; 6:30-9:00 p.m. 16 hrs. $120. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., 333 N. Prairie, Inglewood 90301. (213) 674-7050, ext. 3427.

April 27—**Controversies in Cardiology.** American Heart Assn., Santa Clara County Chapter, at Le Baron Hotel, San Jose. Friday. 6 hrs. $30. Contact: Harriet M. Schutte, RN, PhD, AHA, Santa Clara Co. Chap., 3003 Moorpark Ave., San Jose 95128.

May 3-5—**Critical Care Cardiology.** PMC. Thursday-Saturday. 18 hrs.

May 4-5—**Selected Aspects of Clinical Neuroendocrinology.** Cedars-Sinai Medical Center, Los Angeles. Friday-Saturday. $75. Contact: Lore Kahane, Rm. 2049, Cedars-Sinai Med. Ctr., Box 48750, Los Angeles 90048.

May 4-6—**Sierra Valley Nuclear Medicine Association.** See Radiology and Pathology, May 4-6.

May 4-6—**Coronary Disease, Exercise Testing and Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton Inn, San Diego. Friday-Sunday. 13 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

May 5—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

May 6-11—**Internal Medicine for the Primary Care Physician.** UCD at Hilton Riviera, Palm Springs. Sunday-Friday. 42½ hrs. $275.

May 11-13—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Sunday. 15 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

May 12—**Controversies in Internal Medicine—3rd Annual Program.** San Jose Health Center at Marriott's Great America, Santa Clara. Saturday. 6 hrs. $40. Contact: Stanley Skillicorn, MD, Dir. of Med. Ed., San Jose Health Ctr., 675 E. Santa Clara, San Jose 95112. (408) 998-3212.

May 12-13—**Management of Thrombo-Embolic Disease in Clinical Practice.** UCLA. Saturday-Sunday. 14 hrs.

May 19-20—**Kidney Disease—19th Annual Symposium.** Kidney Foundation of So. Calif. at South Coast Plaza Hotel, Costa Mesa. Saturday-Sunday. Contact: Kidney Foundation of So. Calif., 1281 Westwood Blvd., Suite 200, Los Angeles 90024. (213) 473-6559.

May 23—**Diabetes Symposium.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Janie Sternal, CME Coordinator, 616 Witmer St., Los Angeles 90017. (213) 488-8123.

June 1-3—**Infectious Disease.** Area Health Education Ctr., UCSF, at Del Monte Hyatt, Monterey. Friday-Sunday. Contact: Remi Barron, Area Health Ed. Ctr., P.O. Box 1611, Salinas 93902. (408) 757-3616.

June 4-8—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

June 9-10—**Practical Cardiology for the Primary Care Physician.** UCLA. Saturday-Sunday.

June 20-22—**Pediatric Gastroenterology.** See Pediatrics, June 20-22.

June 21-23—**Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Thursday-Saturday. Contact: Mary Anne McInerny, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 27-29—**Hepatobiliary Disease in Clinical Practice.** PMC at Holiday Inn on Union Square, San Francisco. Wednesday-Friday. 15 hrs. $180.

July 13-15—**Cardiac Symptoms, Arrhythmias and Holter Monitoring.** International Medical Education Corp. at Hyatt, Anaheim. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

July 19-20—**New Approaches to Immunosuppression.** PMC at Fairmont Hotel, San Francisco. Thursday-Friday. 12 hrs. $100.

July 23-24—**Microcirculatory Approach to Current Medical and Surgical Problems.** Microcirculatory Society and American Heart Assn., Greater Los Angeles Affiliate, at Hilton, San Diego. Monday-Tuesday. 14 hrs. $175, before April 1; $200, thereafter. Contact: Nomi Feldman, Conf. Coordinator, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

July 27-29—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Sunday. 15 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

July 30-August 3—**Endocrinology and Metabolism.** UCSF at Hyatt Regency, San Francisco. Monday-Friday.

August 4—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

OBSTETRICS AND GYNECOLOGY

April 15-21—**Current Dialogues in Obstetrics and Gynecology.** Memorial Hospital Medical Center of Long Beach and Women's Hospital of Long Beach at Kauai Surf, Kalapaki Beach, Hawaii. One week. 22 hrs. $300. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 9—**Hormones and Hormone Therapy.** LLU. Wednesday. 4 hrs.

May 21-23—**Recent Advances in Obstetrics and Gynecology.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 18 hrs. $250.

PEDIATRICS

March 15-18—**Clinical Pediatrics—Combined Southern California Pediatric Postgraduate Meeting.** American Academy of Pediatrics, Calif. Chap. 2, at Riviera Hotel, Palm Springs. Thursday-Sunday. Contact: Eve Black, AAP, Calif. Chap. 2, P.O. Box 2134, Inglewood 90305. (213) 757-1198.

April 6-7—**Practical Pediatric Endocrinology.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. 9 hrs. $65.

May 5—**Pediatric Dermatology Seminar.** See Medicine, May 5.

May 7-11—**Pediatric Review—9th Annual.** USC. Monday-Friday.

May 9-11—**Care of the Sick Newborn.** Memorial Hospital Medical Center, Long Beach. Wednesday-Friday. 18 hrs. $125. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 10-12—**Annual Pediatric Course.** UCSF at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

May 12-19—**Pediatric Workshop.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 28 hrs. $325.

May 26-28—**Practical Problems in Pediatrics.** American Academy of Pediatrics, No. Calif. Chapter 1, at Del Monte Hyatt, Monterey. Saturday-Monday. $100, members; $125, nonmembers. Contact: Karen Brown, 604 Fortress Isle, Alameda 94501. (415) 523-3760.

June 16—**Update of Pediatric Ophthalmology.** See Surgery, June 16.

June 20-22—**Pediatric Gastroenterology.** UCSF. Wednesday-Friday.

August 4—**Pediatric Dermatology Seminar.** See Medicine, August 4.

PSYCHIATRY

March 17—**Community Treatment of Schizophrenia.** Mental Research Institute, Palo Alto. Saturday. $60. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

March 23-24—**Techniques of Family Therapy: A Broad Spectrum Approach.** Mental Research Institute. Palo Alto. Friday-Saturday. $100. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

March 23-25—**Clinical Management of Anxiety and Stress.** USC at Rancho Bernardo Inn, San Diego. Friday-Sunday. 13 hrs. $100.

March 27—**Continuing Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

April 7, 21—**The Family as Patient: Case Studies in Family Therapy.** UCLA. Two Saturdays.

April 9-12—**Practical Aspects of Family Therapy.** Mental Research Institute, Palo Alto. Monday-Thursday. $100. Contact MRI, 555 Middlefield Rd., Palo Alto 94301.

April 24—**Continuing Medical Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

April 28—**Dance/Movement Therapy: The Window to Analogic Communication.** Mental Research Institute, Palo Alto. Saturday. $50. Contact MRI, 555 Middlefield Rd., Palo Alto 94301.

May 19—**Community Treatment of Schizophrenia.** Mental Research Institute, Palo Alto. Saturday. $60. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

May 29—**Continuing Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

June 1-2—**Psychosocial Care of the Dying Patient.** UCSF. Friday-Saturday.

June 1-3—**Infant Psychiatry II.** UCSF. Friday-Sunday.

June 8-10—**Family Therapy—Approaches and Techniques.** Cedars-Sinai Med. Ctr., Thalians Community Mental Health Ctr., and So. Calif. Psychiatric Soc. at Beverly Hilton, Beverly Hills. Friday-Monday. 15½ hrs. Contact: Ellen G. Ruderman, LCSW, Thalians Community Memorial Health Ctr., 8730 Alden Dr., Los Angeles 90048. (213) 855-3403.

June 13—**Diagnosis and Office Management of Anxiety and Stress.** LLU. Wednesday. 4 hrs.

June 16-23—**Comparative Psychotherapies.** USC at Royal Lahaina, Maui, Hawaii. One week. 26¾ hrs. $300.

RADIOLOGY AND PATHOLOGY

March 17-18—**Ultrasound.** UCSF at Hyatt on Union Square, San Francisco. Saturday-Sunday.

March 24—**The Abdomen and G.I. Tract—Update 1979.** See Medicine, March 24.

March 29-30—**Cardiovascular Nuclear Medicine.** See Medicine, March 29-30.

April 7—**Imaging.** UCLA. Saturday.

April 18—**Society of Nuclear Medicine, Southern California Chapter—Annual Benedict Cassen Memorial Lecture Dinner Meeting.** L.A. Co. Med. Assn. Headquarters, Los Angeles. Wednesday. Contact: Jean Lynch, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

April 19-20—**Radiology Seminar—Clinical Problems.** UCSF. Thursday-Friday.

May 3-4—**Radiology Seminar—Clinical Problems.** UCSF. Thursday-Friday.

May 4-6—**Sierra Valley Nuclear Medicine Association—11th Annual Spring Symposium.** Northern Calif. Chapter, Society of Nuclear Medicine, at MGM Grand Hotel, Reno. Friday-Sunday. Contact: Cathy Suey, Nuclear Medicine, 4301 X St., Sacramento 95817.

May 19—**Emergency Radiology.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7½ hrs. $50.

May 19-20—**Pathology of the Endocrine System.** UCLA at Long Beach Convention Center. Saturday-Sunday.

June 14-15—**Modern Gastrointestinal Radiologic Techniques for the Practicing Physician.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Friday. 13 hrs. $200.

June 17-22—**Pathology of the Lung.** UCSD at Summer House Inn, La Jolla. Sunday-Friday. 50 hrs. $450.

July 28-August 4—**Medical Imaging.** American College of Medical Imaging at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 15 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

March 17—**Cataract Surgery and Intraocular Lens Implantation Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $225. Contact: Mrs. Lu Hendricks, Jules Stein Eye Inst., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

March 23-25—**Workshop in Soft Tissue Surgery.** UCI at Registry Hotel, Irvine. Friday-Sunday. 20 hrs. $200.

March 29-30—**International Symposium on the Larynx.** See Medicine, March 29-30.

March 29-30—**Diseases of the Urinary Tract.** STAN at Rickey's Hyatt House, Palo Alto. Thursday-Friday. 16 hrs. $200.

April 3-5—**American Laryngological, Rhinological and Otological Society—Annual Meeting.** Century Plaza, Los Angeles. Tuesday-Thursday. 10½ hrs. $40. Contact: R. L. Ruggles, MD, Exec. Sec., 2954 Dorman Rd., Bromall, PA 19008.

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April 5-7—**General Surgery.** UCSF at Sheraton Palace, San Francisco. Thursday-Saturday.

April 8-11—**U.S. Intraocular Lens Symposium.** American Intraocular Implant Society at Century Plaza Hotel, Los Angeles. Sunday-Wednesday. Contact: Kenneth J. Hoffer, MD, P.O. Box 3140, Santa Monica 90403.

April 11—**Diagnosis of the Acute Abdomen.** LLU. Wednesday. 4 hrs.

April 13-14—**Operative Arthroscopy.** UCLA. Friday-Saturday. 12¼ hrs. $315.

April 18-20—**Vitrectomy.** UCSF. Wednesday-Friday.

April 19-20—**Neuro-Ophthalmology—10th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. 16 hrs. $225. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Inst., UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

April 19-21—**Wound Management Workshop.** UCSD, Div. of Plastic Surgery, at Islandia Hyatt House, San Diego. Thursday-Saturday.

April 19-21—**Advances in Clinical Neurourology.** American Urological Assn. at Hyatt Regency, San Francisco. Thursday-Saturday. 16 hrs. $200, members; $250, nonmembers. Contact: Jean Greiner, AUA Office of Education, P.O. Box 1129, Aspen, CO 81611. (303) 925-2012.

April 27-29—**Surgical Update.** UCD at Hyatt Lake Tahoe, Incline Village. Friday-Sunday. 9¼ hrs.

April 29-May 11—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Antonio De La Cruz, MD, Course Dir., ERI, 256 S. Lake St., Los Angeles 90057.

May 1-4—**24th Annual Samuel Higby Camp Lectureship and 14th Annual Scientific Program of the Leroy C. Abbott Orthopaedic Society.** UCSF. Tuesday-Friday. 14 hrs. Contact: Jana S. Smith, Alumni Sec., Univ. of Calif., Rm. U471, San Francisco 94143. (415) 666-1166.

May 10-11—**Surface Replacement.** UCLA. Thursday-Friday.

May 17-18—**Office Orthopedics.** USC. Thursday-Friday.

May 26—**Retinal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Jules Stein Eye Inst., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

May 31-June 1—**Neurosurgery—9th Annual Postgraduate Course.** UCSF at Hilton Hotel, San Francisco. Thursday-Friday.

June 3-15—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Antonio De La Cruz, MD, Course Dir., ERI, 256 S. Lake St., Los Angeles 90057.

June 14-16—**Highlights of Ophthalmology.** PMC. Thursday-Saturday. 15 hrs.

June 16—**Update of Pediatric Ophthalmolofy.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $75. Contact: Mrs. Lu Hendricks, Jules Stein Eye Inst., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

July 23-24—**Microcirculatory Approach to Current Medical and Surgical Problems.** See Medicine, July 23-24.

August 4-11—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 28 hrs. $325.

OF INTEREST TO ALL PHYSICIANS

March 18-22—**Current Issues in Sexuality in Medical Practice.** UCSF at Yosemite. Sunday-Thursday.

March 22-25—**Basic Clinical Hypnosis Workshop—3rd Annual.** UCI at Balboa Bay Club, Newport Beach. Thursday-Sunday.

March 23-25—**Clinical Management of Anxiety and Stress.** See Psychiatry, March 23-25.

March 24—**The Abdomen and G.I. Tract—Update 1979.** See Medicine, March 24.

March 26-28—**Psychiatry for Non-Psychiatrists.** UCSD at Hilton Hotel, San Diego. Monday-Wednesday. 19 hrs. $210.

March 29—**Sexually Transmissible Diseases.** CMA Task Force on Venereal Disease, Calif. VD Controllers' Assn., Riverside Co. Med. Assn. and Calif. Academy of Preventive Medicine at Mission Inn, Riverside. 4 hrs. $12. Contact: Karin McGhee, CMA.

March 29-31—**Contemporary Management of Acute Myocardial Infarction by the Family Physician.** See Medicine, March 29-31.

March 31-April 1—**Symposium on Aging—2nd Annual.** UCSF at Sheraton-Palace, San Francisco. Saturday-Sunday. Contact: UCSF, Cont. Ed. in Health Sciences, 1343 3rd Ave., San Francisco 94143. (415) 666-3904.

March 31-April 1—**Major Sexually Transmitted Diseases: Biology, Host Response, Diagnosis, Epidemiology and Treatment.** UCLA. Saturday-Sunday.

April 5-7—**West Coast Counties Postgraduate Institute.** CMA and UCD at Doubletree Inn, Monterey. Thursday-Saurday. 13 hrs. $60, CMA members; $90, nonmembers. Contact: Charlotte Newhart, CMA.

April 19-21—**San Joaquin Valley Counties Postgraduate Institute.** CMA and UCSD at Ahwahnee Hotel, Yosemite. Thursday-Saturday. 14 hrs. $60, members; $90, nonmembers. Contact: Charlotte Newhart, CMA.

April 21—**Diagnostic Imaging for Primary Care Physicians.** PMC. Saturday. 6 hrs. $65.

April 21-22—**How Primary Care Physicians Can Enhance Their Patients' Health.** UCLA. Saturday-Sunday.

April 23-25—**The Body Fluids in Health and Disease.** UCSF. Monday-Wednesday.

April 28-May 5—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $325.

April 29-May 4—**American Occupational Medical Association—Annual Meeting.** Disneyland Hotel, Anaheim. Sunday-Friday. 16½ hrs. $45, members; $65, nonmembers. Contact: Howard N. Schulz, Exec. Dir., AOMA, 150 N. Wacker Dr., Chicago 60606. (312) 782-2166.

May 4-5—**Providence Hospital Annual Spring Seminar.** Oakland. Friday-Saturday. Contact: Nancy Hansen, Coordinator, Med. Staff Services, Providence Hospital, 3012 Summit St., Oakland 94623. (415) 835-4500, ext. 373.

May 6-11—**Internal Medicine for the Primary Care Physician.** See Medicine, May 6-11.

May 15-21—**Diving Medicine, Basic.** UCSF at VA Hospital, Fresno. One week.

May 18-19—**UCSF—Alumni Day Program.** Friday-Saturday.

May 19-20—**Basic Skills in Sexual Counseling.** UCLA. Saturday-Sunday.

May 20-25—**Fingers-to-the-Toes: An Orthopedic Approach for the Family Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf. Sunday-Friday. 42½ hrs. $280.

May 25-26—**Tropical Disease in the U.S.—Current Views on Diagnosis, Treatment and Epidemiology.** UCSF. Friday-Saturday.

June 1-2—**Psychosocial Care of the Dying Patient.** See Psychiatry, June 1-2.

June 7-9—**Metabolic and Nutritional Care of the Hospitalized Patient.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Saturday.

June 8-9—**Management of Medical Problems.** PMC. Friday-Saturday. 15 hrs.

June 11-16—**Family Practice Refresher Course.** UCI at South Coast Plaza Hotel, Costa Mesa. One week. 46 hrs. $290.

June 18-22—**Family Practice Symposium.** UCSD at Islandia Hyatt, San Diego. Monday-Friday.

June 23-30—**Manipulative Medicine.** USC at Sheraton-Waikiki, Hawaii. One week. $325.

July 19-21—**Tissue Fluid Pressure and Composition.** UCSD. Thursday-Saturday. 17 hrs. $190.

August 4-11—**Hypnosis and Imagery: Practical Applications.** Bay General Community Hosp., Chula Vista, at Hotel Intercontinental, Maui, Hawaii. One week. 15 hrs. $150. Contact: Errol R. Korn, MD, 480 4th Ave., Suite 409, Chula Vista 92010. (714) 420-8051.

August 11-22—**Postgraduate Refresher Course—22nd Annual.** USC at Honolulu and Maui or Kauai, Hawaii. Two weeks. 39 hrs. $325.

August 19-25—**Family Practice Refresher Course—7th Annual.** UCD at Del Monte Hyatt, Monterey. One week. 30 hrs. $225.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

OREGON

COUNCIL ON MEDICAL EDUCATION

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, 97213.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

May 2-6—**Oregon Academy of Family Physicians Annual Meeting.** Valley River Inn, Eugene. Contact: Skippie Patterson, Oregon Academy of Family Physicians, 2153 SW Main, Portland 97205.

PEDIATRICS

May 10-12—**Oregon Pediatric Society Annual Meeting.** Red Lion Downtown, Portland. Contact: Edward L. Hendricks, MD, 12270 SW First St., Beaverton 97005.

OF INTEREST TO ALL PHYSICIANS

Circuit Course Programs—Contact: Joyce Gullixson, Oregon Medical Association, 5210 SW Corbett Avenue, Portland 97201.

April 11 (Roseburg)—**Urology.** Douglas Community Hospital, 1:30 p.m.

April 12 (Coos Bay)—**Urology.** Thunderbird Courtel, 1:30 p.m.

March 28-31—**Common Sense in Comprehensive Care—30th Annual Western Institute on Epilepsy.** Thunderbird Motor Inn, Jantzen Beach, Portland. Contact: Bette Stokes, Epilepsy Association of Oregon, 718 West Burnside, Portland 97209.

March 30-April 1—**Endocrinology.** Salishan Lodge, Gleneden Beach. Contact: J. S. Reinschmidt, MD, Dept. of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

April 4-6—**1979 School of Medicine Alumni Association Scientific Meeting.** University of Oregon Health Sciences Center, Portland. Contact: Mary Ann A. Lockwood, School of Medicine Alumni Association, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

April 19-20—**Dermatology for the Non-Dermatologist.** Red Lion, Jantzen Beach, Portland. Contact: J. S. Reinschmidt, MD, Dept. of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

April 26-27—**Oregon Heart Association Annual Scientific Session.** Red Lion, Portland Center, Portland. Contact: Audrey Booth, Oregon Heart Association, 1500 SW 12th Avenue, Portland 97201.

June 4-6—**Update: Emergency Medicine.** Salishan Lodge, Gleneden Beach. Contact: Richard A. Tuscher, DO, 2900 SE Steele St., Portland 97202.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

March 14-17—**Advances in Pediatrics—118th Meeting North Pacific Pediatric Society.** Wednesday through Saturday. Four Seasons Hotel, Vancouver, BC. Contact: North Pacific Pediatric Society, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121. (206) 623-4801.

March 15-16—**Internal Medicine.** Thursday-Friday. St. Joseph Hospital, Tacoma. Contact: Maxine Bailey, College of Medical Education, 1500 North Warner, Tacoma, WA 98416. (206) 756-3152.

March 17-24—**Orthopaedics (Basic) and Orthopaedics (Advanced).** Saturday through Saturday. Both at Sun Valley, Idaho. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-0150.

March 19—**The Kidney in Health and Disease.** Monday, 4:30-9:30 p.m. Northwest Hospital, Seattle. Contact: Education Dept., Northwest Hospital, 1551 North 120th, Seattle, WA 98133. (206) 364-0500, ext. 686.

March 19—**Osteoporosis and Metabolic Bone Disease and Bone Disease Scanning.** Monday, Wenatchee. 7:30-9:30 p.m. Wenatchee Valley Clinic. Contact William McKee, MD, Wenatchee Valley Clinic, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 19-23—**Advances in Family Practice.** Monday-Friday. Seattle. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 20—**Infectious Diseases—Univ. of Wash. OB-GYN Sessions** (Spokane). Tuesday, 12-1 p.m., Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

March 21—**A Day of Pediatrics.** Wednesday. Mary Bridge Children's Hospital, Tacoma. Contact: Maxine Bailey, College of Medical Education, 1500 North Warner, Tacoma, WA 98416. (206) 756-3152.

March 23-25—**Advanced Cardiac Life Support, Providers Course.** Friday 6-9 p.m.—Saturday—Sunday. North Seattle Community College, Seattle. Contact: Ron Rutherford, Course Coordinator, North Seattle Community College, 9600 College Way North, Seattle, WA 98103. (206) 634-4482.

March 24—**Developmentally Delayed Child.** Saturday. Seattle. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 26-27—**Breast Cancer.** Monday- Tuesday. Swedish Hospital Medical Center, Seattle. Contact: John L. Wright, MD, Swedish Hospital Medical Center, 747 Summit Ave., Seattle, WA 98104. (206) 292-2265.

March 26-27—**Nutrition 1979—Univ. of Wash. Internal Medicine Review Sessions.**

March 26, Wenatchee. Monday, 7:30-9:30 p.m. Wenatchee Valley Clinic. Contact: William McKee, MD, Wenatchee Valley Clinic, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

March 27, Yakima. Tuesday, 5-7 p.m. Memorial Hospital. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

April 2-13—**Rehabilitation Medicine Review.** Two-week course, Seattle. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 5-7—**8th Annual Refresher Course in Diagnostic Radiology.** Spokane, Thursday-Saturday. Sacred Heart Medical Center. 24 hrs. Contact: Marvin J. Gottschall, MD, Sacred Heart Medical Center, West 101 Eighth Ave., Spokane, WA 99204. (509) 455-3330.

April 7—**Mason Clinic Day.** Saturday. Virginia Mason Medical Center, Seattle. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

April 9-13—**Obstetrics/Gynecology Review.** Monday-Friday. Hyatt Regency, Waikiki, Hawaii. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 10—**Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday, 12-1 p.m., Sacred Heart Medical Center. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

April 16-21—**Spanish for Health Professionals.** Seattle, Monday-Saturday. U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 17—**Intrauterine Growth and Retardation—Univ. of Wash. OB-GYN Sessions** (Spokane). Tuesday, 12-1 p.m. Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

April 20-22—**Advanced Cardiac Life Support, Providers Course.** Seattle, Friday 6-9 p.m.—Saturday—Sunday. North Seattle Community College. Contact: Ron Rutherford, Course Coordinator, North Seattle Community College, 9600 College Way North, Seattle WA 98103. (206) 634-4482.

April 21—**Wenatchee Valley Clinic Day.** Wenatchee, Saturday. Wenatchee Valley Medical Clinic. 7 Prescribed hrs. Contact: Gerald E. Gibbons, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

April 23-24—**Drug Interactions—Univ. of Wash. Internal Medicine Review Sessions.**

April 23—Monday, Wenatchee. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, Wenatchee Valley Clinic, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

April 24, Tuesday, Yakima. 5-7 p.m., Memorial Hospital. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

April 26—**Management of Hypertension.** Seattle, Thursday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 28—**Medicine—Tacoma General Hospital Day.** Tacoma, Wednesday. Tacoma General Hospital. Contact: Maxine Bailey, College of Medical Education, 1500 North Warner, Tacoma, WA 98416. (206) 756-3152.

May 3-4—**Medical Alumni Days.** Seattle, Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 4-5—**Medical Applications of Real Time Ultrasound.** Seattle, Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 7-8 **Management of Birth Defects.** Seattle, Monday-Tuesday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 11—**Participation Seminar: Management of Cirrhosis of the Liver.** Seattle, Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 14-15—**Immunoglobulins and Immunologic Disease—Univ. of Wash. Internal Medicine Review Sessions.**

May 14, Monday, Wenatchee. 7:30-9:30 p.m. Wenatchee Valley Clinic. Contact: William McKee, MD, Wenatchee Valley Clinic, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 15, Tuesday, Yakima. 5-7 p.m., Memorial Hospital. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

May 15—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday, 12-1 p.m., Sacred Heart Medical

Center, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

May 18-19—**Radiology.** White Pass Mountain Resort, Friday-Saturday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 19—**Upper Extremity Orthopedics in Primary Care.** Seattle, Saturday. Group Health Cooperative of Puget Sound. Contact: Office of Education, Group Health, A-5, 201 16th Avenue E., Seattle, WA 98112. (206) 326-7348.

May 19-20—**Extracapsular Cataract Surgery and Artificial Lens Implantation: The Northwest Course.** Bellevue, Saturday-Sunday. Overlake Hospital. Contact: David J. McIntyre, MD, Northwest Microsurgical Institute, Inc., 1035 116th Ave., NE, Bellevue, WA 98004. (206) 454-7912.

May 22—**Gynecologic Cancer—Univ. of Wash. OB-GYN Sessions** (Spokane). Tuesday, 12-1 p.m., Sacred Heart Medical Center, Spokane. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 31 and June 1—**Respiratory Care.** Seattle, Thursday-Friday. Contact U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 1—**Management of Acute Surgical Problems.** Seattle, Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 2-3—**Colon and Rectal Surgery.** Seattle, Saturday-Sunday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 7-8—**Surgery.** Seattle, Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 21-23—**American College of Cardiology: Medical and Surgical Management of Coronary Artery Disease.** Seattle, Thursday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 23-24—**The American Medical Heritage: Hematic, Heroic and Heretical.** Sun Valley, Idaho, Saturday-Sunday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 25-26—**Platelets and Clotting—Univ. of Wash. Internal Medicine Review Sessions.**

June 25—Monday, Wenatchee. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, Wenatchee Valley Clinic, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

June 26, Tuesday, Yakima. 5-7 p.m., Memorial Hospital. Contact: Harry Kimball, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

ALASKA, MONTANA AND IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

April 25—**Gynecologic Oncology—Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

May 10—**Consultation With the Alaskan Native Child—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: Robert F. Kraus, MD, Star Route A, Box 26-B, Anchorage, AK 99507. (907) 344-7863.

June 27—**Diabetes in Pregnancy—Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

MONTANA

March 28-30—**An Approach to the Cutaneous Manifestations of Internal Malignancy—Univ. of Wash. Internal Medicine Review Sessions.**

March 28, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

March 29, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

March 30, Friday, Missoula. 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

April 6-7—**Montana Medical Association Scientific Assembly.** Helena, Friday-Saturday. Colonial Inn. Contact: G. Brian Zins, Exec. Dir., Montana Medical Association, 2021 Eleventh Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

April 11-12—**Pediatric Pathology: Role of the Laboratory in Pediatric Diagnosis—Test Selection and Interpretation—Univ. of Wash. Pediatrics Sessions.**

April 11, Wednesday, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 12, Thursday, Whitefish. 11:30 a.m.-1 p.m., North Valley Hospital. Contact: Ronald Miller, MD, 4th and Baker, Whitefish, MT 59937. (406) 862-2515.

April 20-21—**Advanced Cardiac Life Support and Critical Care for Physicians and Nurses.** Kalispell, Friday-Saturday. Outlaw Inn. Contact: Jack L. Davis, MD, 210 Sunnyview Lane, Kalispell, MT 59901. (406) 755-7406.

April 25-27—**Coronary Artery Disease: Medical and Surgical Therapy—Univ. of Wash. Internal Medicine Review Sessions.**

April 25, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 26, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

April 27, Friday, Missoula. 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

May 16-17—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions.**

May 16, Wednesday, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 17, Thursday, Kalispell. 11:30 a.m.-1 p.m., Kalispell Hospital. Contact: Ronald Miller, MD, 4th and Baker, Whitefish, MT 59937. (406) 862-2515.

June 6-8—**Acute Respiratory Failure and Health Effects of Asbestos—Univ. of Wash. Internal Medicine Review Sessions.**

June 6, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

June 7, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

June 8, Friday, Missoula. 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: June 6-8, 1979, Shee Atika Lodge, Sitka.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 25-29, 1979, Safari Hotel, Scottsdale.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 9-12, 1979, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 19-23, 1979, the Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 8-12, 1979, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: June 20-23, 1979, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 4-6, 1979, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 18-20, 1979, Ely Convention Center, Ely.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 2-4, 1979, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Meeting of House of Delegates: April 20-22, 1979, Valley River Inn, Eugene. Annual Scientific Meeting: November 2-4, 1979, OMA Headquarters.

Utah State Medical Association—42 S. 5th East St., Salt Lake City 84102. Annual Meeting: September 11-14, 1979, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 4-7, 1979, Washington Plaza Hotel, Seattle.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: August 28-31, 1979, Jackson Lake Lodge, Moran.

June 21-23—**Montana Academy of Family Physicians' 29th Annual Scientific Assembly.** Fairmont Hot Springs. Thursday-Saturday. Contact: R. Bruce Beithon, MD, Twin Bridges, MT 59754. (406) 684-5642.

IDAHO

March 19—**Infectious Disease—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391.

March 20—**Neonatal Biology—Univ. of Wash. Pediatrics Sessions.**

March 20, Tuesday, Pocatello. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

April 12—**Dizziness, Syncope, Loss of Consciousness and Amnesia—Univ. of Oregon Circuit Course** (Boise). Thursday. 1-5 p.m., Anderson Center. Contact: Ada County Medical Education Consortium, 190 East Bannock, Boise, ID 83702. (208) 386-2135.

April 16—**Intrauterine Growth and Retardation—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391.

April 17—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions.**

April 17, Tuesday, Pocatello. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

April 27-28—**Idaho OB-GYN Society Meeting.** Boise, Friday-Saturday, Sheraton Downtown Inn. Contact: Gloria Stone, P.O. Box 2668, Boise, ID 83701. (208) 344-7888.

May 21—**Gynecologic Cancer—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital, Boise. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391.

May 22—**Pediatric Pathology: Role of the Laboratory in Pediatric Diagnosis—Test Selection and Interpretation—Univ. of Wash. Pediatrics Sessions.**

May 22, Tuesday, Pocatello. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 E. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

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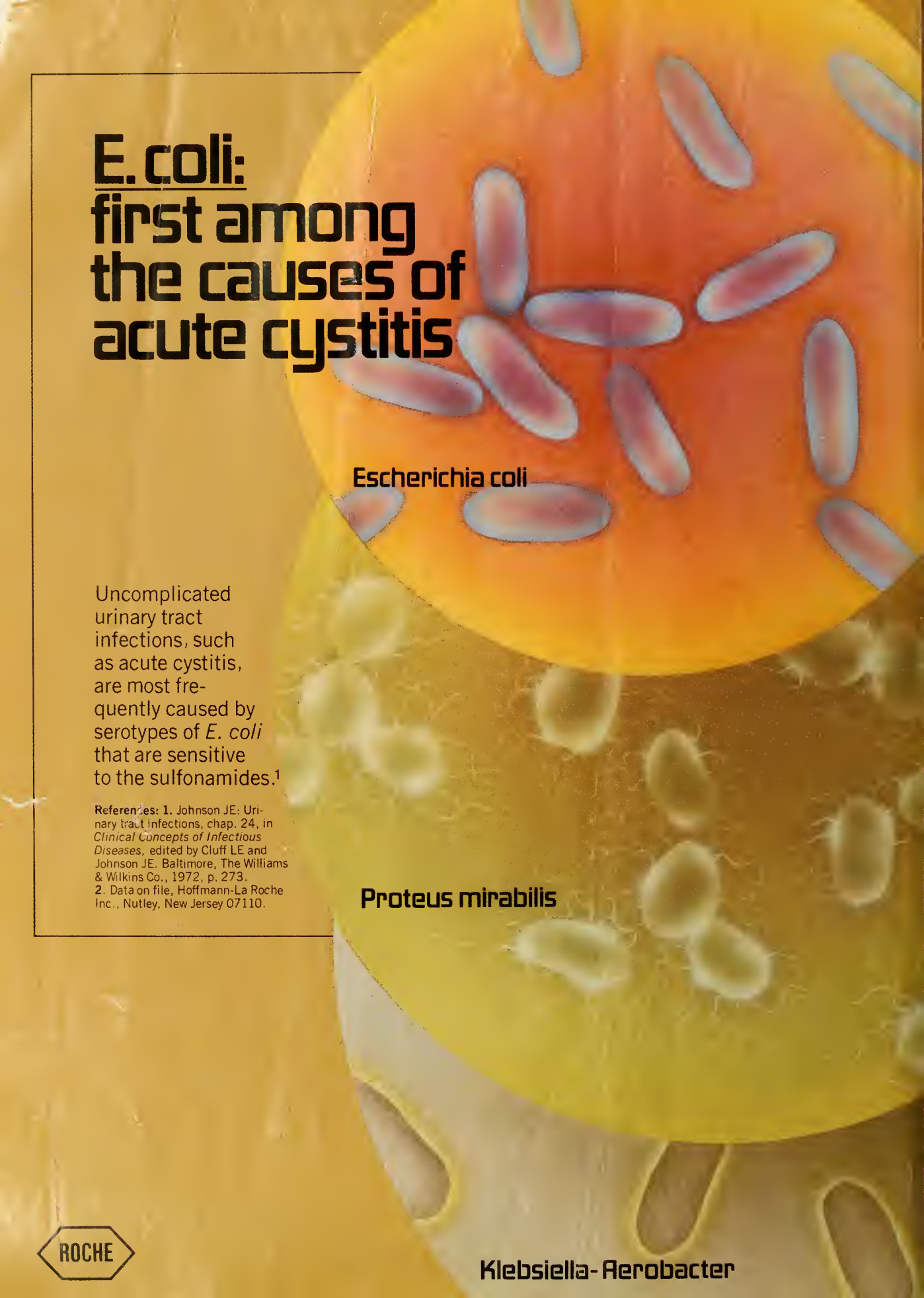
(See Advertising Page 33)

★★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association**

E. coli: first among the causes of acute cystitis



Uncomplicated urinary tract infections, such as acute cystitis, are most frequently caused by serotypes of *E. coli* that are sensitive to the sulfonamides.[1]

References: 1. Johnson JE: Urinary tract infections, chap. 24, in *Clinical Concepts of Infectious Diseases*, edited by Cluff LE and Johnson JE. Baltimore, The Williams & Wilkins Co., 1972, p. 273.
2. Data on file, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter,* staphylococcus, *Proteus mirabilis* and, less frequently, *Proteus vulgaris*), in the absence of obstructive uropathy or foreign bodies. Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections. Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis). *Usual adult dosage:* 2 Gm (2 DS tabs or 4 tabs or 4 teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

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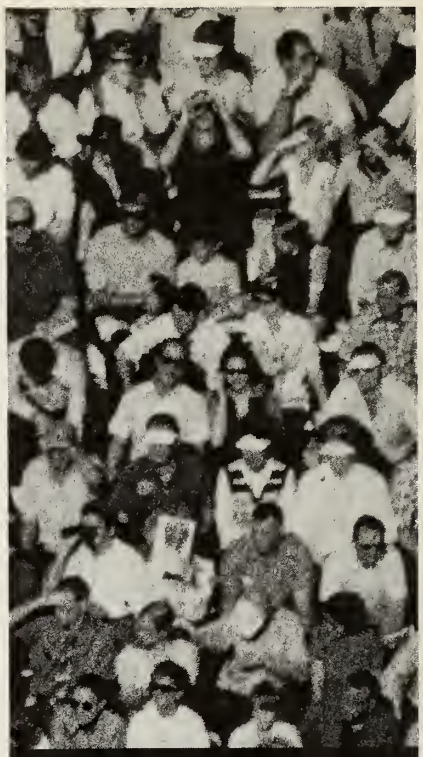

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* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in postsympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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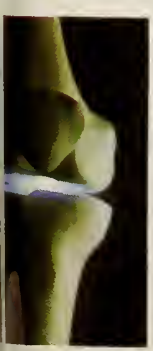
The evidence of experience

Since October 1974 when Motrin® (ibuprofen) was introduced in the United States, it has been used by more than 6,000,000 patients with rheumatoid arthritis* or osteoarthritis. Rarely has an ethical pharmaceutical product been prescribed for so many patients in so short a time. In addition, more than 450 studies presenting new data related to Motrin have been published.

The 6,000,000 patients already treated with Motrin is an objective measure of physicians' confidence in the ability of Motrin to relieve the pain and inflammation associated with rheumatoid arthritis and osteoarthritis.

So it is not surprising that in this short period Motrin has become the most frequently prescribed alternative to aspirin. Motrin relieves joint pain and inflammation as effectively as indomethacin or aspirin, but causes significantly fewer CNS and milder GI reactions. However, gastrointestinal bleeding, sometimes severe, has been associated with Motrin, aspirin, indomethacin, and other nonsteroidal antiarthritic agents.

*The safety and effectiveness of Motrin have not been established in patients with Functional Class IV rheumatoid arthritis (incapacitated, largely or wholly bedridden, or confined to wheelchair; little or no self-care).



Motrin 400 mg TABLETS
ibuprofen, Upjohn

The confidence that comes from experience—
one more reason to prescribe Motrin.

Please turn page for a brief summary of prescribing information.

Upjohn The Upjohn Company, Kalamazoo, Michigan 49001

The confidence that comes from experience—
one more reason to prescribe

Motrin 400 mg TABLETS
ibuprofen, Upjohn

Indications and Usage: Treatment of signs and symptoms of rheumatoid arthritis and osteoarthritis during acute flares and in long-term management. Safety and efficacy have not been established in Functional Class IV rheumatoid arthritis.

Contraindications: Individuals hypersensitive to it, or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory agents (see WARNINGS).

Warnings: Anaphylactoid reactions have occurred in patients with aspirin hypersensitivity (see CONTRAINDICATIONS).

Peptic ulceration and gastrointestinal bleeding, sometimes severe, have been reported. Ulceration, perforation, and bleeding may end fatally. An association has not been established. Motrin should be given under close supervision to patients with a history of upper gastrointestinal tract disease, only after consulting ADVERSE REACTIONS.

In patients with active peptic ulcer and active rheumatoid arthritis, nonulcerogenic drugs, such as gold, should be tried. If Motrin must be given, the patient should be under close supervision for signs of ulcer perforation or gastrointestinal bleeding.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue Motrin and the patient should have an ophthalmologic examination, including central visual fields.

Fluid retention and edema have been associated with Motrin; use with caution in patients with a history of cardiac decompensation.

Motrin can inhibit platelet aggregation and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and those on anticoagulant therapy.

Patients should report signs or symptoms of gastrointestinal ulceration or bleeding, blurred vision or other eye symptoms, skin rash, weight gain, or edema.

To avoid exacerbation of disease or adrenal insufficiency, patients on prolonged corticosteroid therapy should have therapy tapered slowly when Motrin is added.

Drug interactions. *Aspirin* used concomitantly may decrease Motrin blood levels. *Coumarin:* Bleeding has been reported in patients taking Motrin and coumarin.

Pregnancy and nursing mothers: Motrin should not be taken during pregnancy or by nursing mothers.

Adverse Reactions

Incidence greater than 1%

Gastrointestinal: The most frequent type of adverse reaction occurring with Motrin (ibuprofen) is gastrointestinal (4% to 16%). This includes nausea*, epigastric pain*, heartburn*, diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of the GI tract (bloating and flatulence). **Central Nervous System:** Dizziness*, headache, nervousness. **Dermatologic:** Rash* (including maculopapular type), pruritus. **Special Senses:** Tinnitus. **Metabolic:** Decreased appetite, edema, fluid retention. Fluid retention generally responds promptly to drug discontinuation (see PRECAUTIONS).

Incidence: Unmarked 1% to 3%; *3% to 9%.

Incidence less than 1 in 100

Gastrointestinal: Upper GI ulcer with bleeding and/or perforation, hemorrhage, melena. **Central Nervous System:** Depression, insomnia. **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme. **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure. **Special Senses:** Amblyopia (see PRECAUTIONS). **Hematologic:** Leukopenia, decreased hemoglobin and hematocrit.

Causal relationship unknown

Gastrointestinal: Hepatitis, jaundice, abnormal liver function. **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities. **Dermatologic:** Alopecia, Stevens-Johnson syndrome. **Special Senses:** Conjunctivitis, diplopia, optic neuritis. **Hematologic:** Hemolytic anemia, thrombocytopenia, granulocytopenia, bleeding episodes. **Allergic:** Fever, serum sickness, lupus erythematosus syndrome. **Endocrine:** Gynecomastia, hypoglycemia. **Cardiovascular:** Arrhythmias. **Renal:** Decreased creatinine clearance, polyuria, azotemia.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine, so alkaline diuresis may be beneficial.

Dosage and Administration: Suggested dosage is 300 or 400 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day.

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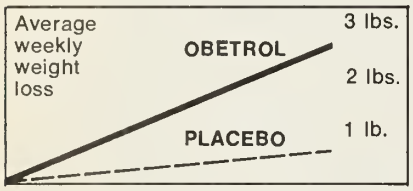
Single entity amphetamine product. Each OBETROL-10 (10 mg. tablet) contains: dextroamphetamine saccharate 2.5 mg., amphetamine aspartate 2.5 mg., dextroamphetamine sulfate 2.5 mg., amphetamine sulfate 2.5 mg. OBETROL-20 (20 mg. tablets) contain twice this potency.

Average weight loss of 2.15 lbs per week compared in clinical studies against a placebo.

CONTROLLED STUDY —
72 CASES 4 WEEKS' RESULTS



Obetrol eases the discomfort of adherence to a restricted diet in individuals who are well motivated to reduce their food intake.

Clinical studies disclose amphetamines to be the most dependable drug in a weight-reduction regimen compared to other anorexigenic agents.

Amphetamines have a significant potential for abuse. In view of their limited short-term anorectic effect and rapid development of tolerance, they should be used with extreme caution and only for limited periods of time in weight reduction programs.

Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
2. Minimal brain dysfunction:
   a. Not recommended for children under 3 years of age.
   b. Children from 3 to 5 years of age: 2.5 milligrams daily, raised in increments of 2.5 milligrams at weekly intervals until optimal response is obtained.
   c. Children 6 years of age and older, 5 milligrams, once or twice daily, increased in increments of 5 milligrams at weekly intervals. Only in rare cases will it be necessary to exceed a total of 40 milligrams per day.
3. Obesity: Usual adult dose 5 to 30 milligrams per day in divided doses.

Overdosage: Manifestations of acute overdosage with amphetamines include restlessness, confusion, assaultiveness, hallucinations, panic states. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension, and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning usually terminates in convulsions and coma.

Management of acute amphetamine intoxication is largely symptomatic and includes lavage and sedation with a barbiturate. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendations in this regard.

Availability: Supplied in bottles of 100; 500 and 1,000 tablets.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

January 1973

Comprehensive informational brochure available upon written request. Prescribe Obetrol for appetite control.

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20 days to shape his world

In essential hypertension, the first 20 days are decisive.

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You can improve those odds. Here's how:

1. COUNSEL: Talk to your patient about the disease and its consequences—about strokes, heart attacks, and kidney failure. Tell him he *must* take medication daily, and for the rest of his life.

2. CATAPRES® (clonidine hydrochloride): because it works, and people stay with it.[2]

Counsel...and Catapres. They can help change the odds against your patient's future.

Please see brief summary of prescribing information on last page of this advertisement for warnings, precautions, and adverse reactions.

Tablets of 0.1 and 0.2 mg

Catapres® (clonidine HCl) can help you shape his world

If you've come to expect only this much of Catapres...

1. smooth lowering of blood pressure
2. effective for all degrees of hypertension (mild to moderate in potency)
3. brain, heart, and kidney blood flow preserved

Ask for more of Catapres

1. no contraindications
2. normal hemodynamics
3. low incidence of depression and orthostatic hypotension
4. no fatal hepatotoxicity
5. excellent record of compliance

Most common side effects are dry mouth, drowsiness and sedation, which generally tend to diminish with time.

Please see brief summary of prescribing information on last page of this advertisement for warnings, precautions, and adverse reactions.

Tablets of 0.1 and 0.2 mg

Catapres® (clonidine HCl)

Hypertension

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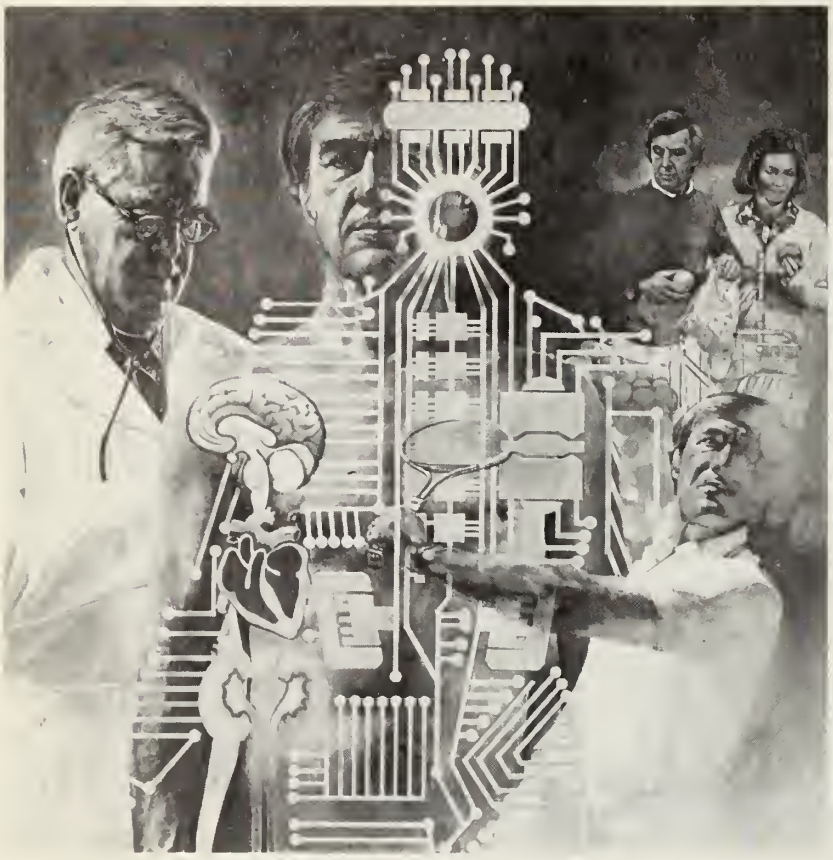

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— A major new film "Compliance: State of the Art"
— A compliance monograph
— Patient Aid Booklet
— Patient Worksheets
— Patient Reminder Postcards
— Other effective compliance enhancers

References:
1. Wilber JA, Barrow JS: Am J Med, *52*:653-663, 1972.
2. Data on file at Boehringer Ingelheim Ltd.

Boehringer Ingelheim

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency It may be employed in a general treatment program with a diuretic and or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported Generally these effects tend to diminish with continued therapy The following reactions have been associated with the drug, some of them rarely (In some instances an exact causal relationship has not been established.) These include Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure, Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes, nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0 1 mg (tan) and 0 2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information

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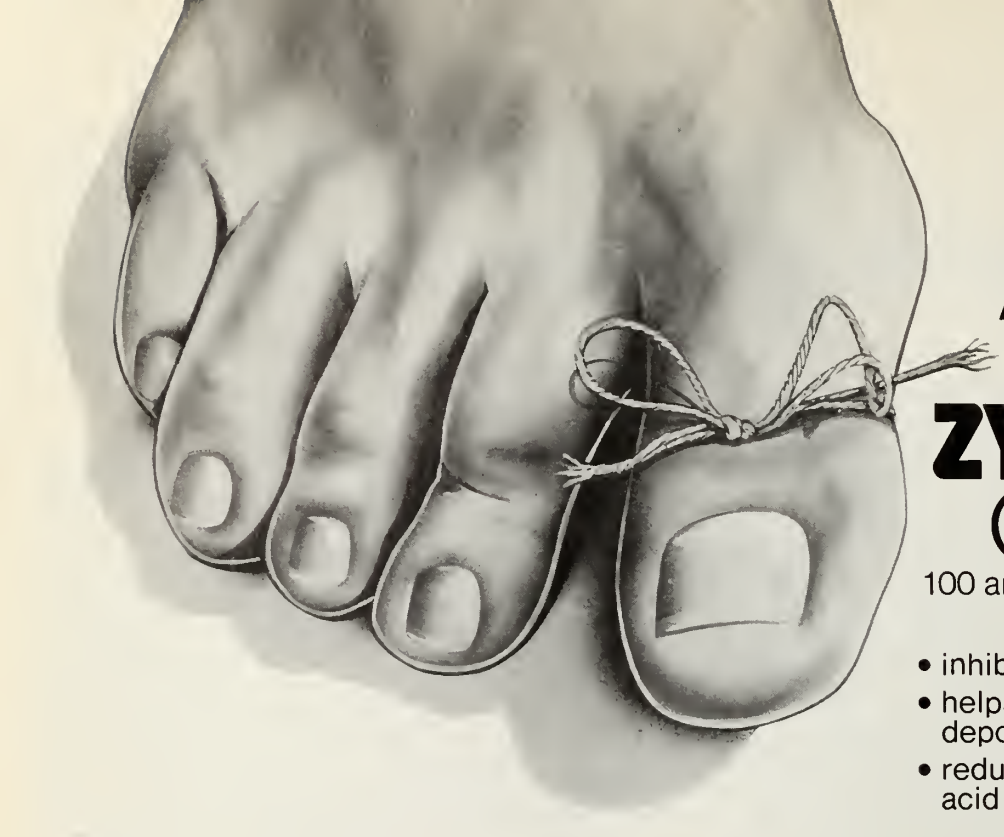

A reminder

ZYLOPRIM®
(allopurinol)

100 and 300 mg scored Tablets

- inhibits uric acid formation
- helps prevent urate crystal depositions in synovia
- reduces risk of uric acid lithiasis

INDICATIONS AND USE: This is not an innocuous drug and strict attention should be given to the indications for its use. Pending further investigation, its use in other hyperuricemic states is not indicated at this time.

Zyloprim® (allopurinol) is intended for:

1. treatment of gout, either primary, or secondary to the hyperuricemia associated with blood dyscrasias and their therapy;
2. treatment of primary or secondary uric acid nephropathy, with or without accompanying symptoms of gout,
3. treatment of patients with recurrent uric acid stone formation;
4. prophylactic treatment to prevent tissue urate deposition, renal calculi, or uric acid nephropathy in patients with leukemias, lymphomas and malignancies who are receiving cancer chemotherapy with its resultant elevating effect on serum uric acid levels.

CONTRAINDICATIONS: Use in children with the exception of those with hyperuricemia secondary to malignancy. The drug should not be employed in nursing mothers.

Patients who have developed a severe reaction to Zyloprim should not be restarted on the drug.

WARNINGS: ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiforme) and very rarely a generalized vasculitis which may lead to irreversible hepatotoxicity and death.

A few cases of reversible clinical hepatotoxicity have been noted and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. Accordingly, periodic liver function tests should be performed during the early stages of therapy, particularly in patients with pre-existing liver disease

Patients should be alerted to the need for due precautions when engaging in activities where alertness is mandatory

Nevertheless, iron salts should not be given simultaneously with Zyloprim. This drug should not be administered to immediate relatives of patients with idiopathic hemochromatosis.

In patients receiving Purinethol® (mercaptopurine) or Imuran® (azathioprine), the concomitant administration of 300-600 mg of Zyloprim per day will require a reduction in dose to approximately one-third to one-fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of Purinethol or Imuran should be made on the basis of therapeutic response and any toxic effects.

Usage in Pregnancy and Women of Childbearing Age: Zyloprim® (allopurinol) should be used in pregnant women or women of childbearing age only if the potential benefits to the patient are weighed against the possible risk to the fetus.

PRECAUTIONS: Some investigators have reported an increase in acute attacks of gout during the early stages of allopurinol administration, even when normal or subnormal serum uric acid levels have been attained.

It has been reported that allopurinol prolongs the half-life of the anticoagulant, dicumarol. This interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

A fluid intake sufficient to yield a daily urinary output of at least 2 liters and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable to (1) avoid the theoretic possibility of formation of xanthine calculi under the influence of Zyloprim therapy and (2) help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

Patients with impaired renal function require less drug and should be carefully observed during the early stages of Zyloprim administration and the drug withdrawn if increased abnormalities in renal function appear.

In patients with severely impaired renal function, or decreased urate clearance, the half-life of oxipurinol in the plasma is greatly prolonged. Therefore, a dose of 100 mg per day or 300 mg twice a week, or perhaps less, may be sufficient to maintain adequate xanthine oxidase inhibition to reduce serum urate levels. Such patients should be treated with the lowest effective dose, in order to minimize side effects.

Mild reticulocytosis has appeared in some patients.

As with all new agents, periodic determination of liver and kidney function and complete blood counts should be performed especially during the first few months of therapy.

ADVERSE REACTIONS:

Dermatologic: Because in some instances skin rash has been followed by severe hypersensitivity reactions, it is recommended that therapy be discontinued at the first sign of rash or other adverse reaction (see WARNINGS). Skin rash, usually maculopapular, is the adverse reaction most commonly reported.
Exfoliative, urticarial and purpuric lesions, Stevens-Johnson syndrome (erythema multiforme) and toxic epidermal necrolysis have also been reported.
A few cases of alopecia with and without accompanying dermatitis have been reported.
In some patients with a rash, restarting Zyloprim (allopurinol) therapy at lower doses has been accomplished without untoward incident.

Gastrointestinal: Nausea, vomiting, diarrhea, and intermittent abdominal pain have been reported.

Vascular: There have been rare instances of a generalized hypersensitivity vasculitis or necrotizing angiitis which have led to irreversible hepatotoxicity and death.

Hematopoietic: Agranulocytosis, anemia, aplastic anemia, bone marrow depression, leukopenia, pancytopenia and thrombocytopenia have been reported in patients, most of whom received concomitant drugs with potential for causing these reactions. Zyloprim® (allopurinol) has been neither implicated nor excluded as a cause of these reactions.

Neurologic: There have been a few reports of peripheral neuritis occurring while patients were taking Zyloprim. Drowsiness has also been reported in a few patients.

Ophthalmic: There have been a few reports of cataracts found in patients receiving Zyloprim. It is not known if the cataracts predated the Zyloprim therapy. "Toxic" cataracts were reported in one patient who also received an anti-inflammatory agent; again, the time of onset is unknown. In a group of patients followed by Gutman and Yü for up to five years on Zyloprim therapy, no evidence of ophthalmologic effect attributable to Zyloprim was reported.

Drug Idiosyncrasy: Symptoms suggestive of drug idiosyncrasy have been reported in a few patients. This was characterized by fever, chills, leukopenia or leukocytosis, eosinophilia, arthralgias, skin rash, pruritus, nausea and vomiting.

OVERDOSAGE: Massive overdosing, or acute poisoning, by Zyloprim has not been reported.

HOW SUPPLIED: 100 mg (white) scored tablets, bottles of 100 and 1000; 300 mg (peach) scored tablets, bottles of 30, 100 and 500. Unit dose packs for each strength also available.

Complete information available from your local B. W. Co. Representative or from Professional Services Department PML.

U.S. Patent No. 3,624,205 (Use Patent)

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The only procainamide in veneer-coated, easy-to-swallow tablets

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See following page for brief summary

PRONESTYL® TABLETS
Procainamide Hydrochloride Tablets

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

DESCRIPTION: Pronestyl (Procainamide Hydrochloride) is the amide analogue of procaine hydrochloride and is available for oral administration as veneer-coated tablets providing 250 mg, 375 mg, and 500 mg procainamide hydrochloride.

CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: Evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with oral maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

ADVERSE REACTIONS: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported in patients on oral maintenance therapy (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

For full prescribing information, consult package insert.

HOW SUPPLIED: Pronestyl Tablets (Procainamide Hydrochloride Tablets) providing 250 mg, 375 mg, and 500 mg procainamide hydrochloride are available in bottles of 100 and Unimatic® single-dose packaging in cartons of 100. The 250 mg and 500 mg tablets are also available in bottles of 1000.

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QUIBRON®

Each capsule or tablespoonful (15 ml) liquid contains theophylline (anhydrous) 150 mg and glyceryl guaiacolate (guaifenesin) 90 mg

- theophylline for effective around-the-clock bronchodilator therapy
- 100% free theophylline

Indications: For the symptomatic relief of bronchospastic conditions such as bronchial asthma, chronic bronchitis, and pulmonary emphysema

Warnings: Do not administer more frequently than every 6 hours, or within 12 hours after rectal dose of any preparation containing theophylline or aminophylline. Do not give other compounds containing xanthine derivatives concurrently.

Precautions: Use with caution in patients with cardiac disease, hepatic or renal impairment. Concurrent administration with certain antibiotics, i.e. clindamycin, erythromycin, troleandomycin, may result in higher serum levels of theophylline. Plasma prothrombin and factor V may increase, but any clinical effect is likely to be small. Metabolites of guaifenesin may contribute to increased urinary 5-hydroxyindoleacetic acid readings, when determined with nitrosonaphthol reagent. Safe use in pregnancy has not been established. Use in case of pregnancy only when clearly needed.

Adverse Reactions: Theophylline may exert some stimulating effect on the central nervous system. Its administration may cause local irritation of the gastric mucosa with possible gastric discomfort, nausea, and vomiting. The frequency of adverse reactions is related to the serum theophylline level and is not usually a problem at serum theophylline levels below 20 mcg/ml.

How Supplied: Capsules in bottles of 100 and 1000 and unit-dose packs of 100; Liquid in bottles of 1 pint and 1 gallon

See package insert for complete prescribing information.

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THE WESTERN
Journal of Medicine

Refer to: Kattus AA, Coulson AH, Karrasch M: Ischemic heart disease—Precarious coronary lesions and prognosis. West J Med 130:293-299, Apr 1979

Ischemic Heart Disease

Precarious Coronary Lesions and Prognosis

ALBERT A. KATTUS, MD; ANNE H. COULSON, *and* MADELINE KARRASCH, DDS, *Los Angeles*

Coronary arteriograms in 113 patients whose cases were followed for 2 to 12 years were analyzed in an attempt to discover why in some patients with angina pectoris there are long stable clinical courses and in others the courses proceed rapidly to death. It was found that patients with completed coronary occlusions, usually with distal portions reconstituted by collateral, had favorable prognoses with prolonged longevity. Patients with multiple high grade narrowings of the coronary arteries, on the other hand, had poor prognoses with high attrition rates. The more stenotic lesions present in the coronary arteries, the higher the attrition rates. Completed coronary occlusions, therefore, have been classified as nonprecarious while local coronary stenoses greater than 50 percent of the lumen diameter have been classified as degrees of precariousness according to the number of lesions present.

When compared with classification by number of diseased vessels and by arteriographic score of Friesinger, the nonprecarious cases had better prognoses than the precarious.

IN SOME PATIENTS with angina pectoris of effort the clinical courses are remarkably prolonged and stable, uncomplicated by coronary events; in others similar clinical characteristics seem to be present but the courses proceed rapidly to death. In the hope of finding an explanation for the wide disparity in the clinical courses among patients with myocardial ischemia, a study was undertaken in which an attempt was made to trace the patients in whom coronary angiography was done in the years between 1960, when we first began to use this technique in our institution, and the year 1971, when bypass graft operations became commonplace. As review of the patient records proceeded and as the old angiograms were studied, it became evident that patients who had long uncomplicated survival despite anginal symptoms and evidence of myocardial ischemia shown on exercise electrocardiograms had coronary arteries with one or more complete obstructions compensated by collateral circulation from unobstructed arterial segments. In those patients whose clinical courses proceeded to early coronary death, angiograms showed high grade narrowings in major coronary arteries with antegrade flow through the stenotic segments.

These observations led to the concept that a completely occluded coronary artery is inherently stable because it cannot worsen and is, therefore, nonthreatening. An occluded artery has the potential for improvement if its collateral flow were

From Division of Cardiology, Department of Medicine, UCLA School of Medicine and Division of Epidemiology, UCLA School of Public Health, Los Angeles. Ms. Coulson is senior statistician in the Division of Epidemiology.

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Submitted, revised, September 1, 1978.

Reprint requests to: Albert A. Kattus, MD, 501 East Hardy St., Suite 404, Inglewood, CA 90307.

ABBREVIATIONS USED IN TEXT
CFX = circumflex coronary artery
LAD = left anterior descending coronary artery
Rt = right coronary artery

to increase or if recanalization of the occluded segment were to occur. Complete coronary occlusion, therefore, might be considered a nonprecarious lesion because it is stable and predictable. Tight stenoses of coronary arteries, on the other hand, are inherently unstable because they are unpredictable. They are likely to progress at some time to complete closure but one cannot predict how or when. If the closure is gradual then collateral channels may have time to develop a compensating blood supply. If, however, closure is abrupt, a coronary event is likely to occur in the form of myocardial infarction or sudden death. Consequently, local stenotic lesions of coronary arteries have come to be regarded by us as precarious, and experience has indicated that the more such lesions there are the higher is the degree of precariousness.

The most commonly used method of grading the severity of coronary obstructive lesions and relating this to prognosis consists of counting the number of major coronary arterial trunks that harbor obstructive lesions (usually 50 percent or more narrowing of the lumen). Cases are classified, therefore, as having one-vessel, two-vessel or three-vessel coronary obstructive disease.[1-3] Actuarial survival curves have been published from several centers showing that one-vessel disease carries a low mortality risk, two-vessel disease a higher risk and three-vessel disease a very high mortality. In this method there is no discrimination between total occlusion and various degrees of stenosis.

Friesinger and his associates[4] have attempted to develop a more discriminating grading system which they have called the coronary angiographic score. A point system is used to rate the severity of the obstructive lesions with five points for total occlusion, ratings from one to four points for varying degrees of partial obstruction and zero for no narrowing. The maximal angiographic score is 15, indicating complete obstruction in all three major coronary arteries. In this system a complete occlusion (regarded by us as nonprecarious) is given a higher score than a tight stenosis (regarded by us as having a degree of precariousness).

Friesinger has presented survival curves showing low mortality for scores 1 to 4, intermediate mortality for scores 5 to 9 and very high mortality for scores 10 to 15.

We were able to trace 113 patients in whom reliable follow-up data could be combined with angiograms of interpretable quality. The angiograms in the cases were reread and classified according to precariousness by the method to be described subsequently. They were also classified according to the number of obstructed vessels and according to the angiographic score. To show the prognosis according to these three methods of classification, actuarial survival curves were constructed.

Patients and Methods

Hospital records were reviewed on 165 patients in whom coronary angiography was done for the study of ischemic heart disease. Patients in whom coronary arteries were visualized incidental to hemodynamic studies of congenital, valvular or myocardiopathy disease were not included. Excluded from the study were nine patients who had large ventricular aneurysms or ventricles so badly damaged that ejection fractions were below 40 percent. Small areas of akinesis or dyskinesis at the sites of healed infarcts were not considered disqualifying. Four patients were excluded because bypass graft operations were carried out less than a year after angiograms were done. Other causes for exclusion were lost angiograms (11 cases), angiograms of uninterpretable quality (7 cases), lost charts or missing information (3 cases), inability to trace patient (18 cases).

Full information was available on 105 men and 8 women ranging in age from 30 to 72 years, with a mean of 50 years. Reason for study in all but nine cases was the presence of chest pain resembling angina pectoris. In two there were ischemic responses on treadmill exercise testing without anginal pain and in seven there was rest angina with good exercise tolerance (Prinzmetal variant angina).[5] Three coronary angiograms in the series were done by the aortic root flushing technique in 1960. Subsequently, angiography and ventriculography were done by the Sones[6] or Judkins[7] technique.

The cineangiograms were all read independently by the senior author and compared with the original radiologic reading. When differences of interpretation arose the disagreements were adjudicated with Julius Grollman, MD, Chief of

Cardiologic Radiology, University of California, Los Angeles, so that all interpretations represented a consensus among at least two readers. Patient follow-up was obtained by personal contact, communication with private physicians, mail questionnaire or telephone communication with the patients.

Determining Degrees of Precariousness

Coronary arteries that were open throughout containing no narrowing greater than 50 percent were considered to have zero degree of precariousness. Also considered nonprecarious were coronary arteries or their primary branches which were totally occluded. This classification held whether or not the vessel was reconstituted by collateral circulation beyond the occlusion. Each stenotic lesion greater than 50 percent in the major coronary arteries or their primary branches was considered one degree of precariousness. A single artery can yield a precariousness greater than one since it may have multiple discrete stenoses. A precarious lesion in the left main coronary artery was given a rating of two degrees because both circumflex and anterior descending systems are jeopardized by such a lesion. A narrowing in a vessel for which another artery which could serve as the source for collateral supply has already been totally occluded is also given a double rating since the reduced availability of collateral supply increases the jeopardy.

Examples of Nonprecarious and Precarious Disease

The concept of the precarious and nonprecarious coronary lesions is best presented by reference to the following examples in which the method of rating according to degree of precariousness is illustrated. The examples also indicate the ratings according to the number of diseased vessels and according to Friesinger's angiographic score.

The prototype for the nonprecarious state is illustrated in Figure 1 which shows the coronary arteriographic findings in a man with nondisabling angina pectoris and pronounced ischemic electrocardiographic changes during treadmill exercise whose case had been followed for eight years of an uneventful clinical course. Study of the angiogram in this case as shown in the diagram discloses that there is complete occlusion of the anterior descending (LAD) and the circumflex (CFX) marginal coronary arteries, both of them reconstituted by retrograde flow from collateral channels fed from the unimpeded right coronary artery. The stable clinical course in this patient is believed to be due to the fact that the obstructive lesions are complete and, therefore, cannot worsen, but they could conceivably improve if collateral flow were to increase or if recanalization were to take place. The complete occlusion is taken to be a nonprecarious lesion because it appears to represent a stable state not likely to change abruptly. In this patient, therefore, there is no precariousness with two-vessel disease. The coronary arteriographic obstruction score of Friesinger is 7 (LAD-5, CFX-2).

The prototype of the precarious coronary circulation is illustrated in Figure 2. This shows coronary angiographic findings in a man with disabling angina who died suddenly one week after the angiogram. The anterior descending coronary artery has a proximal high grade stenosis and the right coronary artery (Rt) is com-

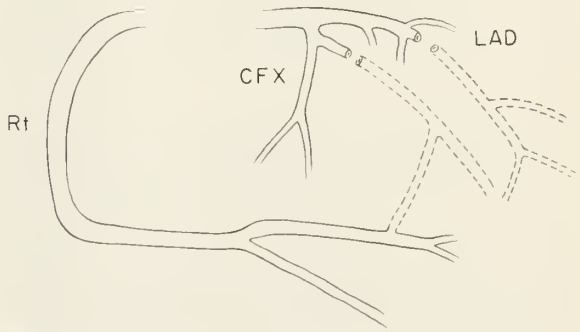

Figure 1.—Diagram of nonprecarious coronary circulation derived from study of selective cineangiograms. Dotted lines indicate vessels reconstituted by collateral flow distal to occlusion. Diagram represents a composite of left anterior oblique view of right coronary and right anterior oblique view of left system. Rt = right coronary, CFX = circumflex, LAD = left anterior descending, LAD and CFX marginal are completely occluded.

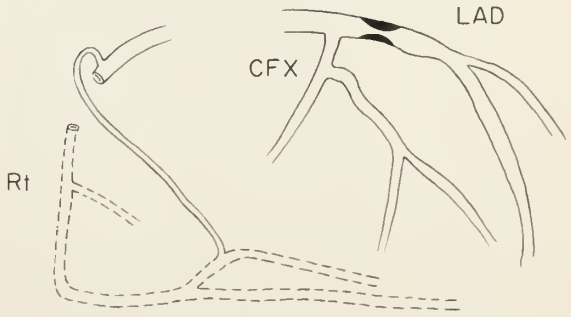

Figure 2.—Diagram of precarious coronary circulation. There is high grade stenosis in left anterior descending coronary artery (LAD) and complete occlusion of right coronary artery (Rt) with reconstitution via collateral channels. CFX = circumflex.

Figure 3.—Diagram of precarious coronary circulation on left. Repeat arteriogram five years later shows closure of one stenotic lesion which produced myocardial infarct. A new stenotic lesion had also appeared in the right coronary.

pletely occluded but filled by bridging collaterals. The pronounced narrowing in the anterior descending is taken to be highly precarious because it is likely to progress to complete occlusion and it cannot be predicted when this might happen or whether it will occur gradually or abruptly. Furthermore, the lesion carries double jeopardy to the anterior myocardium because its major possible source of collateral flow is already eliminated by total occlusion of the right. In this case there is two-vessel disease with two degrees of precariousness; coronary arteriographic score 8 (Rt-5, LAD-3).

In Figure 3 are illustrated two coronary angiograms taken five years apart on a 46-year-old man who was first disabled by angina, improved on an exercise training program and subsequently had a nonfatal myocardial infarction. The first angiogram made during severe angina disability showed two pronounced stenoses in the right coronary artery and one in the anterior descending coronary artery representing three degrees of precariousness, one for each local stenotic lesion. Four years after the first angiogram an anteroseptal myocardial infarction occurred without warning. In a subsequent repeat coronary angiogram it was shown that the anterior descending coronary artery had closed at the site of the previous local stenosis. The two right coronary stenoses previously seen remained unchanged, but a new stenosis had appeared in the distal right coronary with poststenotic dilatation beyond. In this man with two-vessel coronary disease there were four distinct points of coronary narrowing, one of which apparently closed abruptly to produce a coronary event. It is reasoned that any one of the four narrow points could have gone on to closure and there was no way to predict which one would do it or when. Hence, we rate this patient as having had four degrees of precariousness before the infarct. Coronary arteriographic score was 5 (Rt-3, LAD-2) on the first angiogram and 8 (Rt-4, LAD-4) on the second.

Data Handling

All coronary angiograms were rated by the three different systems described. Considering the day on which the angiogram was done as time zero, survival curves were constructed by age-adjusted actuarial methods.[8] Only the cases of patients who died from coronary causes are included in the attrition rates. There were 37 cardiac-related deaths in the series and 2 due to noncardiac causes. The deaths from cardiac causes are tabulated in Table 1. Nine of the deaths were related to surgical attempts at revascularization, six to bypass vein grafting, one to Vineberg in-

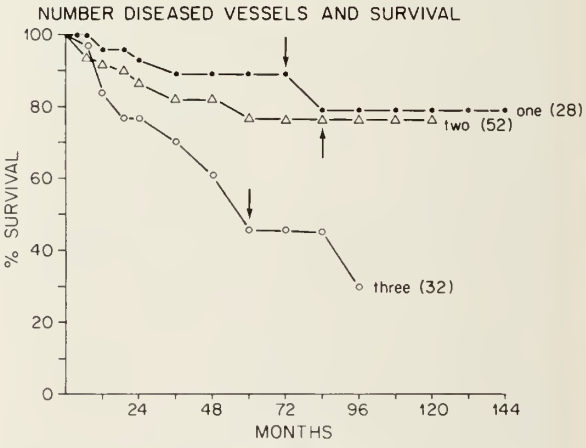

Figure 4.—Survival curves actuarially computed based on one-, two- and three-vessel coronary obstructive disease. Number of patients in each group in parentheses at right. Vertical arrows indicate the interval in months at which the number of subjects drops below ten.

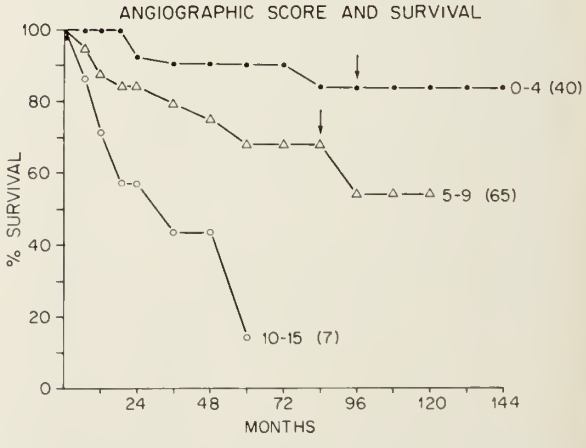

Figure 5.—Survival curves based on angiographic score. Number of patients in each group in parentheses at right. Vertical arrows indicate the interval at which the number of subjects drops below ten.

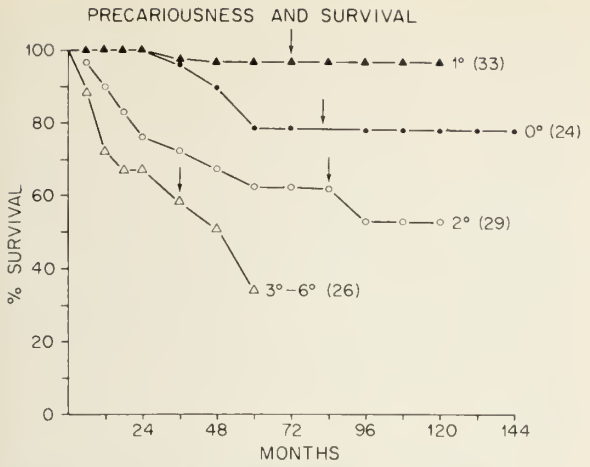

Figure 6.—Survival curves based on degrees of precariousness. Number of patients in each group in parentheses at right. Vertical arrows indicate the interval at which the number of subjects drops below ten.

ternal mammary implantation procedures and one to coronary endarterectomy. The interval between the initial catheterization and operation in these patients ranged from 12 to 103 months; the average was 40 months. Two deaths also occurred during heart catheterization and these are regarded as cardiac deaths and included in the survival curves. Deaths resulting from attempted coronary revascularization operations are not included as coronary deaths because presumably the patients would have survived longer if the operations had not been carried out. The cases of these patients and also those of patients lost to follow-up are treated as though the period of follow-up terminated when the patients were last known to be alive. The cases of six patients in whom revascularization operations were done successfully are also classified as though the period of follow-up ended on the day of the operation. The interval between initial catheterization and operation in these patients averaged 63.7 months with range from 27 to to 96 months.

In view of the limited size of the study population (a total of 113 patients), the survival curves shown should be interpreted in terms of the consistency of trends, and only cautiously in terms of the absolute shape of the curve. Axtell[9] indicates that survival rates are not acceptable where fewer than ten cases enter the interval alive, and should be interpreted with care where less than 50 cases enter the interval alive. The number of cases in each subgroup entering the study is shown in Figures 4 through 8. In Figures 4, 5 and 6 vertical arrows indicate the interval in months at which the number of subjects drops below ten for each classification group and subgroup included in the survival curves. A life table procedure for analyzing longitudinal studies described by Fleiss and co-workers[10] was used to test for the significance of the difference between two series of probabilities.

Results

Survival curves for the three different rating methods are shown in Figures 4, 5 and 6. Attrition rates for the classifications by number of diseased vessels and by the angiographic score are comparable to those published by others.[1-4] The attrition rates for the various degrees of precariousness follow expected trends for degrees 2

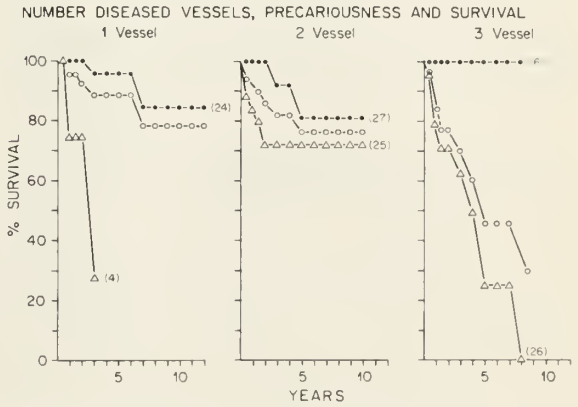

Figure 7.—Survival curves for patients with one-, two- and three-vessel obstructive disease. Open circles represent the whole group as seen in Figure 4. Closed circles are those with zero or one degree of precariousness. Triangles are those with two to six degrees of precariousness.

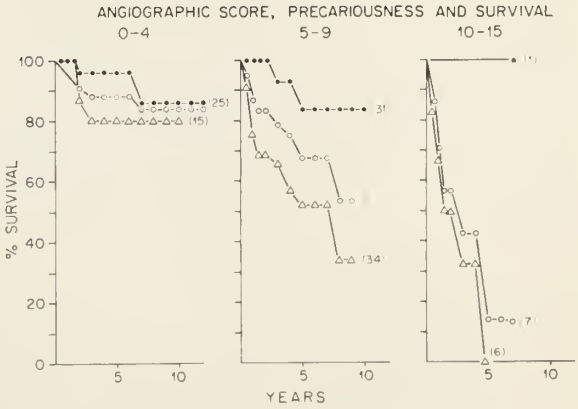

Figure 8.—Survival curves for patients classified by angiographic score. Open circles represent whole group as in Figure 5. Closed circles represent those with zero or one degree of precariousness. Triangles represent those with two to six degrees of precariousness.

and above. Unexpected is the observation that the one-degree precarious group fared better than the zero-degree group. However, this difference is not statistically significant. Therefore, the zero-degree and one-degree groups can be combined to constitute a single low-risk group. (Table 1)

Each group of patients classified by the number of diseased vessels and by the arteriographic score method may be subdivided into two populations, precarious and nonprecarious. Considering those with zero and one degree as nonprecarious and those with two to six degrees as precarious, each of the number of diseased vessel and arteriographic score classes has been subdivided into precarious and nonprecarious populations and survival curves plotted as in Figures 7 and 8. In each instance the precarious group has a higher mortality than the nonprecarious group. Of particular interest is the group of six nonprecarious patients with three-vessel coronary disease with no mortality over eight years of observation.

Despite the relatively small numbers, these differences in trend between the precarious and nonprecarious groups were significant over the first two-year period for one- and two-vessel disease ($p<.05$). In one-vessel disease no further evaluation was possible. Five- and ten-year trends for two-vessel disease were not significantly different. Trends for three-vessel disease were significant over the three-, five- and ten-year periods ($p<.05$, $<.01$ and $<.01$, respectively). In the three angiographic score groups the difference in trends was not significant in the low score group but was consistently significant ($p<.01$) in the intermediate group. In the high score group the numbers were too small to allow testing.

Discussion

The findings in this historical prospective study support the concept that the completed coronary closure is a nonprecarious obstructive lesion that is predictable and compatible with a long uncomplicated clinical course even though ischemic manifestations may be present. Local stenotic lesions, on the other hand, are found to be precarious because they are associated with high risk of mortality, and the more there are of such lesions the higher is the risk.

TABLE 1.—*Mortality and Degrees of Precariousness*

Degrees of Precariousness	*No. of Cases*	*Coronary Deaths*	*Mortality Percent*	*Manner of Death*			
				Sudden Death	*Myocardial Infarct*	*Operative*	*Cath*
0	24	6	25	3	1	2 BP	..
1	33	2	6	..	..	1 END	..
						1 VB	
Low precarious (0-1)	57	8	14				
2	29	12	41	4	7	1 BP	..
3	16	8	50	4	1	2 BP	1
4-6	11	9	82	3	3	2 BP	1
High precarious (2-6)	56	29	52				
Totals	113	37	32.7	14	12	9	2

BP = bypass vein graft END = coronary endarterectomy VB = Vineberg implant

TABLE 2.—*History of Coronary Artery Lesions Seen in Sequential Coronary Angiograms—25 Cases*

	Right Coronary	*Circumflex*	*Anterior Descending*	*Total*
Complete occlusions stable	11	5	6	22
Average patient months*	35	44	32	..
Stable stenosis	5	6	10	21
Average patient months	44	42	33	..
Progressive narrowing	17	7	8	32
Average patient months	38	48	44	..
New disease	8	1	4	13
Preexisting stenosis	9	6	4	19
Total closure	5	5	2	12
Number with myocardial infarction	1	0	1	2

*Average time per patient between first and second angiogram.

The method of assigning degrees of precariousness has purposely been kept simple in order to test its validity. The only weighting of the precarious lesion has been to double its value in left main lesions and in cases in which a possible source of collateralization has already been obliterated. This fails to take into consideration the higher risk of anterior descending lesions which have been shown to have increased mortality.[11,12] The very high risk of the left main coronary lesion[13] is confirmed by our finding that eight of 14 patients with that lesion had died, with an average survival time of 15 months. Of six surviving patients, revascularization procedures were done successfully in three.

It was not possible to trace the distribution of standard coronary risk factors such as blood cholesterol levels, blood pressure, smoking habits and carbohydrate tolerance among the precarious and nonprecarious groups because many of these cases were studied long before the significance of risk factors was understood. However, we believe that the risk factors are probably distributed randomly through the study population because the subjects all had established coronary obstructive disease at entry into the study. The only characteristic that separated them into precarious and nonprecarious was whether obstructive lesions were incomplete or complete.

A striking feature of the survival curves in all three of the methods of analysis—number of vessels, angiographic score and precariousness—is the wide divergence of the various categories in the first five years, with survival leveling off at that point in all but the most severely diseased. The implication is that after the first five years the disease becomes less active and the chance of death decreases. The reason for this trend might be that once coronary stenotic lesions become narrow enough to cause myocardial ischemia and thereby make the disease symptomatically evident, closure is likely to occur within five years, producing a coronary event if closure is abrupt but allowing collateral adaptation if closure proceeds gradually. Once the adaptation has been attained, an inherently stable nonprecarious state may permit long-term survival. The previously precarious state tends to evolve into a state of clinical stability.

Suggestive evidence that progression from the incomplete threatening lesion to the completely closed collateralized lesion was found when we studied the sequential angiograms of the 25 patients in our study in whom two coronary angiograms were done at least one year apart. The findings are listed in Table 2. Over three to four years, 60 percent of the stenotic lesions became narrower (32 of 53). Twelve of these 32 lesions went to complete closure but only two of them produced myocardial infarction. The other ten closed without producing a coronary event. Most of the closures, therefore, were associated with physiologic adaptations that changed a high-risk state to a low-risk state, from precarious to nonprecarious.

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Refer to: Hayden GF, Meyers JD, Dixon RE: Nosocomial varicella—Part II. Suggested guidelines for management. West J Med 130:300-303, Apr 1979

Nosocomial Varicella

Part II: Suggested Guidelines for Management

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Because of the potential severity of varicella among patients with compromised immunity in hospitals, a case of nosocomial varicella demands immediate attention. Patients with varicella should be discharged or placed in strict isolation. Other patients in the hospital should be screened for varicella exposure and susceptibility, and isolated as necessary. Exposed staff members must also be screened for susceptibility. Prompt institution of these measures should prevent or reduce transmission of nosocomial varicella.

THE SEVERITY OF VARICELLA in patients with impaired immunity was illustrated by Part I of this article (Meyers JD, MacQuarrie MB, Merigan TC, et al: Nosocomial varicella—Part I: Outbreak in oncology patients at a children's hospital. West J Med 130:196-199, Mar 1979). The congregation of such patients in hospital wards and "therapeutic communities" creates a dangerous, potentially explosive situation, and the occurrence of varicella in this setting demands a prompt response to interrupt or prevent transmission. The lack of published guidelines for such action reflects underlying uncertainty about the appropriate response, since no approach has been shown to be effective in controlled studies. However, this lack of data does not reduce the urgency of the situation. Although decisions about the isolation techniques to be employed are largely judgmental rather than based on experimental evidence, decisions must be implemented nonetheless. This report outlines a proposed response to a case of nosocomial varicella. This approach is not intended to be accepted and used without question, but rather as a working model to be modified as new data allow and as individual circumstances require.

Care of Patients With Active Varicella

Patients with varicella should be discharged from the hospital immediately if medically possible. Those who cannot be discharged should be placed under strict isolation (private room with no recirculation or cross-circulation of air, and the use of gowns, gloves and masks for persons entering the room[1]). If otherwise appropriate, two or more patients with varicella may share the same room.

Other Patients in the Hospital

The care of other patients in the same hospital with a patient with an active case of varicella is shown schematically in Figure 1.

Screening for Susceptibility to Varicella

Patients in the hospital should be classified as susceptible or immune on the basis of historical information supplemented with serologic screening when possible. Historical susceptibility can be ascertained quickly but may be inaccurate. Most children with histories of previous varicella are immune, while most with negative or unknown histories are susceptible, but exceptions to this rule occur. For example, Ross observed a 7 per-

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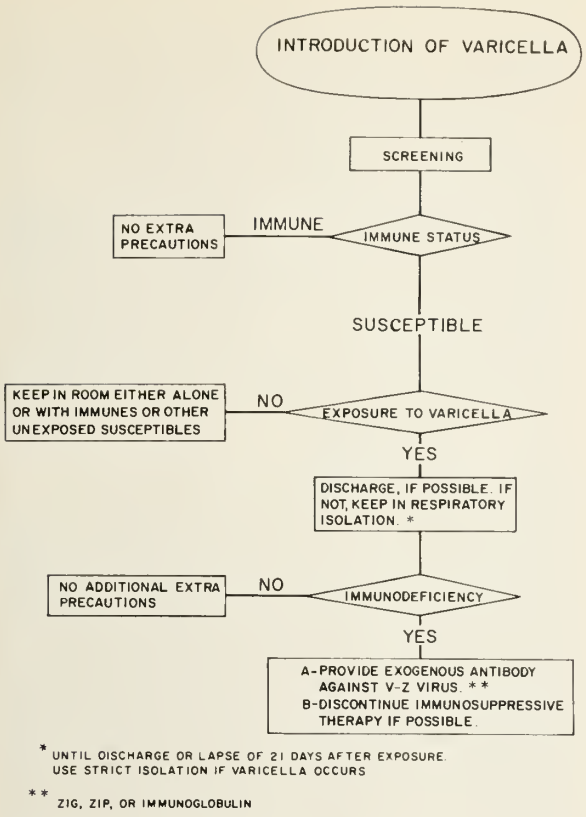
INTRODUCTION OF VARICELLA
SCREENING
IMMUNE STATUS
IMMUNE
NO EXTRA PRECAUTIONS
SUSCEPTIBLE
EXPOSURE TO VARICELLA
NO
KEEP IN ROOM EITHER ALONE OR WITH IMMUNES OR OTHER UNEXPOSED SUSCEPTIBLES
YES
DISCHARGE, IF POSSIBLE. IF NOT, KEEP IN RESPIRATORY ISOLATION. *
IMMUNODEFICIENCY
NO
NO ADDITIONAL EXTRA PRECAUTIONS
YES
A-PROVIDE EXOGENOUS ANTIBODY AGAINST V-Z VIRUS. **
B-DISCONTINUE IMMUNOSUPPRESSIVE THERAPY IF POSSIBLE.
* UNTIL DISCHARGE OR LAPSE OF 21 DAYS AFTER EXPOSURE. USE STRICT ISOLATION IF VARICELLA OCCURS
** ZIG, ZIP, OR IMMUNOGLOBULIN

Figure 1.—Care of hospital patients exposed to active varicella.

cent varicella attack rate among historically immune children after household exposure to varicella, compared with an 87 percent attack rate among children with negative or unknown histories.[2] Subclinical varicella is considered unusual, but may account for false-negative histories.

Immediate isolation measures must be based on historical information. However, when available, serologic screening should be employed to define susceptibility more precisely. Testing for complement fixing antibody against varicella-zoster virus is often available through reference laboratories, but titers frequently revert to undetectable levels months to years after varicella-zoster infection.[3] Despite the common occurrence of false-negative results, positive titers are suggestive of immunity; though titers as low as 1:4 are considered positive in some laboratories,[4] a minimum titer of 1:8 is more commonly employed. Testing for fluorescent antibody to membrane antigen (FAMA) against varicella-zoster virus[5,6] is less readily available, but titers are more durable and therefore more reliable in screening for susceptibility. Other methods, such as immune adherence hemagglutination[7] and the immunoperoxidase modification of the FAMA test[8] may also be useful if available locally.

Classification of Patients as Exposed or Unexposed

In view of the high communicability of varicella, a liberal definition of exposure should be employed. In general, any patient on the same ward as a patient with active varicella should be considered exposed. Exposures may also occur in playrooms, x-ray departments and other locations in a hospital. At a minimum, the period of contagiousness should include one day before rash onset until the crusting of all vesicles, usually four to six days after rash onset. Patients may rarely be infectious as early as four days before onset,[9] and the period of contagiousness may be prolonged in patients with compromised immunity in whom lesions continue to appear.[10]

Isolation of Susceptible Patients

Exposed susceptible patients should be discharged immediately if medically possible. Patients who cannot be discharged should be placed in respiratory isolation (private room with no recirculation or cross-circulation of air, handwashing on entering and leaving the room, and use of masks for persons entering the room) until discharge, onset of varicella or 21 days after the last exposure to varicella. Discharge may be postponed with some degree of safety up to seven days after rash onset in the index case, since an exposed susceptible person in whom varicella later develops will usually not be contagious this soon; this calculation is based on a minimum incubation period of ten days, with infectivity beginning one day before rash onset in both the index and secondary cases. The incubation period may be prolonged in patients treated with exogenous varicella-zoster antibody shortly after exposure,[11,12] so respiratory isolation of such patients should be continued for at least 28 days. Unexposed susceptible patients should be placed in single rooms or in rooms with immune patients or other unexposed susceptible patients.

Exposed Susceptible Persons With Compromised Immunity

Exposed susceptible persons with compromised immunity should receive exogenous antibody against varicella-zoster virus as soon as possible after exposure, preferably within 72 hours. The preferred agents for use in prophylaxis are zoster immune globulin and varicella-zoster immune

globulin. Alternate methods include use of zoster immune plasma and pooled, standard immunoglobulin (formerly immune serum globulin).

Zoster immune globulin is hyperimmune globulin prepared from plasma of healthy persons with recent herpes zoster infection, whereas varicella-zoster immune globulin is prepared from pooled plasma containing high titers of varicella-zoster antibody. Both are available from the Sidney Faber Cancer Institute, Boston, Massachusetts, on a limited basis for postexposure prophylaxis of varicella in children with impaired immunity who fulfill strict criteria concerning age, degree of immunodeficiency, and time and intimacy of exposure.[13]* When given within 72 hours of exposure, zoster immune globulin has been shown to prevent varicella in normal children.[14] Current evidence suggests that it is effective in modifying or preventing varicella in children with impaired immunity.[11,12,15-18] There is no evidence that zoster immune globulin is effective therapeutically in children in whom clinical varicella has already developed.

Zoster immune plasma also appears to prevent or modify infection.[6,19,20] If zoster immune globulin or varicella-zoster immune globulin cannot be obtained, and titered plasma cannot be located through local or regional blood banks, one may be able to identify an otherwise healthy adult who is convalescing from herpes zoster and is willing to donate plasma. Since rapid prophylaxis is essential, fresh plasma must often be given before determining its varicella-zoster antibody titer. Titers are generally highest one to four weeks following zoster infection, but there is considerable variation in height of antibody response, and the varicella-zoster antibody titer of the plasma should be checked after administration, if not before. The arbitrary recommended dose is 10 ml per kg of body weight, with a maximum dose of 250 ml (1 unit). The plasma should be checked for evidence of hepatitis B surface antigen before administration.

When zoster immune globulin, varicella-zoster immune globulin or zoster immune plasma is not available, some physicians choose to administer standard immunoglobulin. When given shortly after exposure, high doses of immunoglobulin seem to modify,[2] but not prevent,[19,21] varicella in normal children. The amount of varicella-zoster antibody in immunoglobulin is not standardized. Very large doses (at least 1 ml per kg of body weight) must be given to approximate the amount of antibody administered with conventional doses of zoster immune globulin, varicella-zoster immune globulin or zoster immune plasma.

In addition to providing exogenous antibody against varicella-zoster virus, it appears beneficial with respect to severity of varicella to discontinue chemotherapy or radiotherapy during the potential incubation period.[22] This may not always be possible, especially in the case of steroids, and this recommendation must be carefully considered on an individual basis.

Care of Staff Members

Screening for Susceptibility to Varicella

Although some exposed staff members may have negative or unknown histories of varicella, most in fact will be immune. Gershon and coworkers[23] found that more than 95 percent of American-born women of childbearing age had detectable antibody to varicella-zoster virus. Even among the historically susceptible women in this group, most were shown to be immune by varicella-zoster-FAMA testing. Ross[2] observed a clinical attack rate of only 8 percent among historically susceptible adults with household exposure. The attack rate among adults with unknown histories was 2 percent. While susceptible staff members may be few in number, attempts should be made to identify such persons. When available, serologic screening will aid in the identification of truly susceptible persons and minimize the possible disruption of medical services.

Isolation of Susceptible Staff

Measures should be taken to protect susceptible staff members from patients with varicella, and to protect susceptible patients from staff members who are incubating varicella. The ideal solution is straightforward: relieve susceptible staff members from duties involving contact with patients with varicella or with susceptible patients. Only immune staff should be allowed to work on a ward in which there is a case of active varicella. Exposed susceptible staff should not care for susceptible patients in the hospital until 21 days after the last possible date of exposure, and should be relieved from all duties at the first sign of illness.

While conceptually simple, this solution may be difficult to implement. Banishment of historical susceptibles from work in involved areas during the chickenpox season could hinder adequate

*These criteria may differ from those discussed in this artcle.

staffing of pediatric wards. Therefore, compromises with the ideal strategy may be necessary. For example, if a susceptible staff member has had only minimal exposure to varicella, one may allow this person to care for immune patients or those with normal host defenses. In addition, some persons negative by history may be considered "more susceptible" than others: New staff should be considered particularly suspect, whereas immunity is more likely in personnel who have long histories of work exposure to pediatric patients with varicella whether or not they recall having had the disease themselves.

Elective Admission of Patients to the Ward

Susceptible patients should not be electively admitted to the ward until 21 days after crusting of all vesicles in the last case of varicella. This allows for elapse of one *maximum* incubation period of 21 days after the end of contagiousness in the last case. Cases occurring after this time are presumably unrelated to the earlier case. The interval should be extended to 28 days if passive immunization has been employed. Immune patients may be admitted unless the needs for increased isolation and cohorting of patients and staff are so great as to overwhelm personnel resources. In this instance, it may be necessary to postpone *all* elective admissions.

Live, Attenuated Varicella Vaccine

Live, attenuated varicella virus vaccine has been developed and tested in Japan. It is well tolerated and has prevented clinical illness among susceptible siblings of children with active varicella when given within three days of exposure.[24,25] The vaccine has also been successful in preventing the spread of varicella among children in hospital and has been administered to several immunocompromised patients without known adverse effects.[26-28] This vaccine is still investigational and many questions remain about its short-term and long-term safety.[29-31] Its future use in the prevention of nosocomial varicella is speculative at this time.

Summary

Because of the potential severity of varicella among patients with compromised immunity in hospital, nosocomial varicella demands immediate attention. This article outlines a suggested approach to this problem: Patients with active varicella should be discharged from the hospital as soon as possible, or placed in strict isolation if discharge is not possible. Other patients in the hospital should be screened for varicella exposure and susceptibility, and isolated as necessary. Susceptible patients with impaired host defenses should be passively immunized if exposed. Exposed staff members should also be screened for the likehood of varicella susceptibility. Prompt institution of these measures should prevent or reduce transmission of nosocomial varicella.

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The Warren Shunt in Treating Bleeding Esophageal Varices

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In patients who have impaired hepatic reserve, the Warren shunt has been proposed as an effective operation because it decompresses the esophageal varices without disturbing portal perfusion of the liver. However, early reports of high operative mortality and technical difficulties have impeded acceptance of the procedure.

The operation was done in a series of 17 patients. All patients in whom elective variceal decompression with a patent splenic vein was required and without clinical ascites were candidates for this operation. Follow-up ranged from 2 to 48 months. Six patients had alcoholic cirrhosis, two had primary biliary cirrhosis and seven had postnecrotic cirrhosis; in two the cause of the liver disease was unknown. Five patients were categorized as Child's class A, nine as class B and three as class C. No intraoperative or early postoperative deaths owing to hemorrhage occurred. However, there was one death two weeks postoperatively from pulmonary sepsis and one death five weeks postoperatively due to antigen-positive hepatitis. Two patients died from hepatic failure six weeks and five months after operation, respectively; in the first of these, chronic active hepatitis was diagnosed at the time of operation. In one patient hemorrhage recurred and transfusion was required. Although ascites, which eventually resolved, developed in eight patients after operation, the results in 76 percent of patients have been good without new episodes of hemorrhage or encephalopathy. We conclude that the Warren shunt is a safe and effective elective operation for the treatment of patients in whom hemorrhage from esophageal varices has occurred.

THE SURGICAL TREATMENT of bleeding esophageal varices by portasystemic shunting is usually successful in arresting hemorrhage but it often produces encephalopathy and has not been conclusively shown to prolong life. Although there are several reasons for the untoward sequelae of total portal diversion, the final common pathway is probably related to diversion of most of the portal blood from an already compromised liver.

In order to minimize the incidence of hepatic failure and encephalopathy after total portal systemic diversion, selective portasystemic shunting procedures are being widely used. Although there are several types of selective shunts, the one pre-

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dominantly employed in the United States is the distal splenorenal shunt proposed by Warren and associates in 1967.

Three basic principles are embodied in the Warren shunt: (1) decompression of the esophagogastric varices via the intact short gastric veins by a shunt created between the distal end of the splenic vein and the side of the left renal vein, (2) maintenance of portal perfusion of the liver and (3) portal azygous disconnection interrupting the coronary, right gastric and right gastroepiploic veins.[12]

Despite the theoretic advantages of this procedure over total portasystemic shunting, the surgical community has been slow to accept the Warren shunt. Technical difficulty in the splenic vein dissection, causing significant operative blood loss, is one reason for this reluctance. Skepticism that this "small" shunt will effectively control esophageal bleeding is another. A third reason is that ascites represents a relative contraindication to the procedure.

Since 1974 we have carried out a distal splenorenal shunt in most patients stabilized after variceal hemorrhage who have had a patent splenic vein shown on angiography and who have not had significant ascites. The distal splenorenal shunt was employed only in elective or semiemergent cases. This report presents our experience with these 17 patients.

Patients and Methods

The series of patients, ranging in age from 15 to 64, comprised eight women and nine men. Cirrhosis was present in all patients: six had alcoholic cirrhosis, two had primary biliary cirrhosis, seven had postnecrotic cirrhosis and two had cryptogenic cirrhosis. All patients had had at least one episode of variceal hemorrhage, and most had had multiple episodes. In 15 patients preoperative endoscopy was done to confirm bleeding varices, and in all of these patients celiac and superior mesenteric angiography with venous phase visualization was carried out to determine the anatomy of the portal system, and specifically the patency of the splenic vein.

A preoperative liver biopsy was done in ten patients to rule out acute hyaline necrosis. If this pathologic diagnosis was made, operation was not considered. However, there were four patients with chronic active hepatitis at the time of operation. Classification of patients according to Child's criteria designated five as class A, nine as class B and three as class C. The prothrombin time was prolonged in ten patients. Although no significant ascites was apparent in any patient at the time of operation, approximately 50 percent of the patients had had significant ascites preoperatively. In four patients there was hepatic encephalopathy preoperatively associated with variceal hemorrhage. Clinical profiles of the entire group are summarized in Table 1.

TABLE 1.—*Summary of Clinical Profiles*

Type of Cirrhosis	*Number of Patients in Child's Classifications*		
	A	*B*	*C*
Alcoholic	1	4	1
Biliary	1	1	..
Postnecrotic ...	2	4	1
Cryptogenic ...	1	..	1

Surgical Technique

The technique employed for the distal splenorenal shunt is essentially the method described by Warren.[11] However, there are several technical points worthy of note: The splenic vein must be at least 8 mm in diameter to assure long-term patency of the shunt. When dissecting the splenic vein from the inferior border of the pancreas, the small pancreatic branches should be tied in continuity and divided or clipped rather than applying clamps which tend to tear these fragile veins. It is important to dissect the splenic vein proximally enough to prevent kinking when the anastomosis is constructed. Excision of a wedge of retroperitoneal tissue between the splenic and renal veins will also facilitate a gentle arc of the splenic vein for an unobstructed anastomosis. In our experience, utilization of the Blalock clamp on the divided splenic vein affords added maneuverability in carrying out the anastomosis. Finally, we are in complete agreement with Warren that the anterior row of the anastomosis should be interrupted to prevent a purse-string effect.[11] Once the anastomosis is finished, it is imperative to effect a complete portoazygous disconnection. This entails ligation of the right gastric, umbilical right gastroepiploic, and coronary veins. Special care must be taken when dividing the coronary veins because failure to accomplish this can cause postoperative hemorrhage or encephalopathy.[14]

Results

Postoperative Survival

Patient follow-up has been excellent in all but one survivor, ranging from 2 to 48 months (mean,

27 months). Although four deaths have occurred in this series, none was attributable to intraoperative bleeding or recurrent variceal hemorrhage. One patient, a Child's class C, died within 30 days of operation. The operation was urgently done for continued bleeding resistant to intravenous vasopressin and balloon tamponade. The patient was recovering from aspiration pneumonia when bleeding began again and was taken to surgery. He died of pulmonary sepsis eight days postoperatively.

There were three late deaths—occurring five weeks, six weeks and five months postoperatively—caused by an antigen-positive fulminating hepatitis, progressive liver failure (in a patient with chronic active hepatitis) and hepatorenal syndrome, respectively. In all of the patients mild upper gastrointestinal bleeding occurred as a terminal event. The data concerning these postoperative deaths are summarized in Table 2.

Postoperative Complications

Among the complications in the surviving patients, ascites has been predominant. In seven patients ascites developed after operation and cleared within two months. One patient (previously reported) had intractable chylous ascites which gradually subsided after nine months of medical management.

Encephalopathy has not been a problem, although two patients had acute encephalopathy in the immediate postoperative period that was easily controlled with neomycin. None has had chronic encephalopathy characterized by persistent neuropsychiatric symptoms such as flapping tremor, alterations in sleep rhythms or mental deterioration. Normal activities were resumed in most cases; in fact, two patients functioned effectively in accounting positions.

Approximately 40 percent of the patients had preoperative evidence of hypersplenism with leukopenia or thrombocytopenia (or both); postoperatively, no consistent alteration in the state of hypersplenism was seen after distal splenorenal shunting.

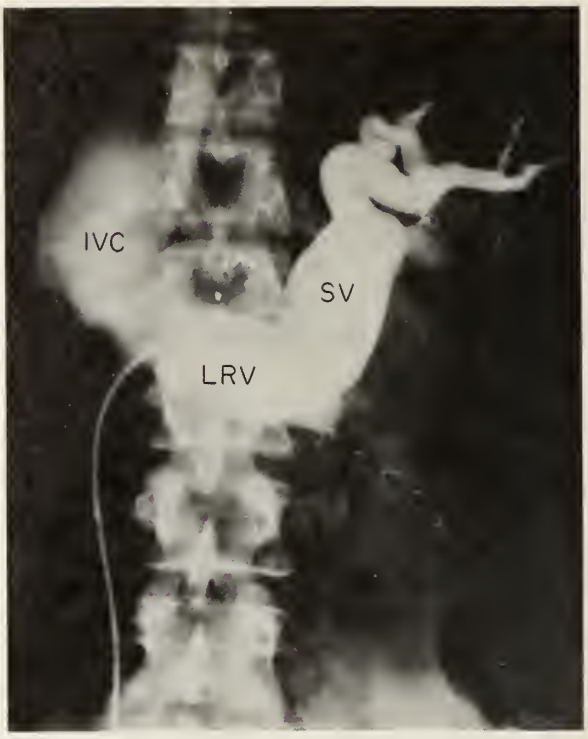

Figure 1.—Angiogram of distal splenorenal shunt. Catheter is in left renal vein. IVC = inferior vena cava. LRV = left renal vein. SV = splenic vein.

To date none of the survivors in this series has had significant upper gastrointestinal hemorrhage. One patient had a small hemorrhage on two occasions (5 months and 12 months postoperatively) which was treated conservatively and diagnosed by endoscopy as gastritis. Postoperative evaluation of varices by upper gastrointestinal series in most patients had disclosed that although varices persist for a significant period of time after operation (6 to 12 months), they eventually decrease in size.

Postoperative angiography has been done in 25 percent of patients; in all cases the shunt was shown to be patent and even significantly larger in diameter with dilatation of the splenic vein (Figure 1).

Comments

A patient in whom gastroesophageal varices develop has a 50 percent to 80 percent chance

TABLE 2.—*Postoperative Deaths*

Death	*Child's Class*	*Operation*	*Cirrhosis*	*Cause of Death*
Operative	C	Emergent	Alcoholic	Pulmonary sepsis and failure
Late	B	Emergent	Alcoholic	Antigen positive hepatitis
Late	B	Elective	Postnecrotic and chronic active hepatitis	Hepatic failure
Late	C	Emergent	Postnecrotic	Hepatic failure and hepatorenal syndrome

of dying with the first variceal hemorrhage, and after the first hemorrhage the prognosis fails to improve.[13]

Despite the effectiveness of portacaval shunting in controlling variceal hemorrhage, its efficacy in prolonging survival has been clearly disclaimed in three prospective randomized studies.[4,6,7] These controlled studies have shown that patients with shunts die of liver failure while the medically treated patients succumb to bleeding. Indeed, the incidence of hepatic encephalopathy was approximately equal in the medically and surgically treated groups. However, severe disabling chronic encephalopathy is more common in those patients who were treated with portasystemic shunt. In a 26-year experience with 404 patients, Voorhees and co-workers[9] found that for surgical cases followed for a period of five years or longer the incidence of encephalopathy was 57 percent.

The concept of the selective distal splenorenal shunt was based on the premise that by maintaining portal venous perfusion and selectively decompressing the gastroesophageal varices, bleeding could be controlled and encephalopathy substantially decreased. This has been borne out in three series of patients in whom the incidence of encephalopathy has been less than 5 percent with a follow-up of 96 months.[2,3,8] This reduction in clinical encephalopathy has been correlated with measurements of maximum urea synthesis.[10] Warren showed that in patients who have had portacaval shunts, maximum urea synthesis rates are significantly reduced shortly after operation, while in those who are treated with the distal splenorenal shunt there is little change. Our own clinical experience has verified this low incidence of encephalopathy after the selective Warren shunt.

Skepticism regarding the Warren shunt as an effective means of preventing recurrent hemorrhage has proved to be unjustified. In previously published series,[2,8,11] as in our experience, documented recurrent variceal hemorrhage has not been apparent, thereby indirectly attesting to the fact that the distal splenorenal shunt is not only large enough to decompress the varices but also has long-term patency. Postoperative angiography obtained in the series reported by Thomford[8] and in our series showed an open shunt in all patients in whom an angiogram was done. Radiographic disappearance of varices in our patients was slow despite the lack of recurrent hemorrhage, a phenomenon previously reported by Hutson and associates.[2]

Carlson and Ehrenfeld[1] described a patient who had recurrent variceal hemorrhage 28 months after a successful Warren shunt; however, in this case the rebleeding may have stemmed from an enlarged coronary vein which was not interrupted at the time of operation. The necessity of carrying out a complete portal-azygous disconnection at the time of shunting has been emphasized by Warren.[11] Failure to completely separate the portal and gastroesophageal areas into two distinct venous water sheds can lead to recurrent hemorrhage and encephalopathy (written communication, 1977, Robert Zeppa, MD, Chairman, Department of Surgery, University of Miami School of Medicine).

Technically, the Warren shunt is a demanding procedure and may take twice the operating time that a portacaval or interposition mesocaval shunt requires, and therefore it has not been recommended for use in cases of uncontrollable massive variceal hemorrhage. In cases where bleeding is slowed but an emergent operation is indicated, the Warren shunt should be considered only if the patient's condition is stable enough for adequate preoperative evaluation to be done, including visceral angiography with venous phase visualization. This is particularly important if reversed portal flow is documented because in such a situation the benefits of the distal splenorenal shunt in preserving hepatoportal flow cannot be realized and a more expeditious shunt procedure must be employed.

Before carrying out a distal splenorenal shunt, adequate preoperative evaluation and preparation of the cirrhotic patient is mandatory. In a patient who is bleeding, initial attempts at pharmacologic control of the portal hypertension with or without the addition of balloon tamponade should be made. In more than 80 percent of our patients, successful temporary control of the bleeding could be obtained, allowing time to improve the patients' conditions. This entails providing nutrition orally, or with restricted sodium l-essential amino acid parenteral feeding; using gentle diuresis to control ascites; controlling acid base and electrolyte abnormalities (especially hypokalemic alkalosis which potentiates the development of encephalopathy) and carrying out a preoperative liver biopsy to rule out acute hyaline necrosis. If acute hyaline necrosis is present, it contraindicates operation because mortality has been shown to exceed 80 percent in such cases.[5] It must be emphasized that medical preparation is an essen-

tial feature in the management of patients who are scheduled for a distal splenorenal shunt inasmuch as the risk of this operation, like that for portacaval shunts, is determined largely by the patient's preoperative status.

The findings in our small series of distal splenorenal shunts as well as those of larger series reported in the literature[2,8,11] have suggested that the Warren shunt can be done with an operative mortality as low as that of a total shunt. Moreover, it is equally as effective as the total shunt in preventing recurrent hemorrhage and has a lower risk of encephalopathy than the total shunt. Whether the Warren shunt will prolong life in cirrhotic patients in whom hemorrhages have occurred is not known because no substantial randomized studies comparing medically treated patients with those in whom Warren shunts were done have been reported. However, in a series of 42 patients with postnecrotic cirrhosis in whom distal splenorenal shunt was done, Zeppa[14] reported an 88 percent probability of survival for six years calculated on an actuarial basis. This is at least twice the rate reported for patients with postnecrotic cirrhosis treated with a total shunt. On the other hand, the survival rate of alcoholic patients was no better than in those treated with a total shunt. These preliminary data suggest that postnecrotic cirrhotic patients may represent a subset of patients in whom there is prolonged survival following distal splenorenal shunt.

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Patients at Risk for Nodular Goiter

IN IDENTIFYING the patient at greatest risk, bear in mind that the neoplasm is more likely to occur in younger patients. It has a higher incidence in the male, and is of more concern in the patient who has a solitary nodule as opposed to multiple nodules, if it's solid and nonfunctioning. I try to differentiate between the patient who has a nonfunctioning or cold nodule and a patient who has one that's warm. This is not always easy to do, but if it's truly cold it places that person at a higher risk; if it's truly warm, it's probably not cancerous.

—COLIN G. THOMAS, JR., MD, *Chapel Hill, North Carolina*

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Specialty Conference

Moderator
HAROLD E. PAULUS, MD

Discussants
HERBERT I. MACHLEDER, MD
PHILIP J. CLEMENTS, MD
KENNETH NYMAN, MD
SEYMOUR LEVINE, MD

An edited transcription of an Interdepartmental Clinical Case Conference arranged by the Department of Medicine of the UCLA School of Medicine (University of California, Los Angeles)

Refer to: Paulus HE, Machleder HI, Clements PJ, et al: Prolonged thoracic-duct drainage in rheumatoid arthritis and systemic lupus erythematosus—Interdepartmental Clinical Case Conference, University of California, Los Angeles (Specialty Conference). West J Med 130:309-324, Apr 1979

Prolonged Thoracic-Duct Drainage in Rheumatoid Arthritis and Systemic Lupus Erythematosus

The thoracic duct was surgically cannulated in nine patients with rheumatoid arthritis and in two patients with systemic lupus erythematosus. Lymph was drained continuously for up to 105 days, lymphocytes were removed by centrifugation and the cell-free lymph was reinfused intravenously. Diversion of thoracic-duct lymphocytes produced a prompt decrease in synovitis and nodule size in rheumatoid arthritis, a diminution of cutaneous vasculitis and proteinuria in systemic lupus erythematosus and a marked drop in IgG serum concentrations. Prolonged thoracic-duct drainage with depletion of recirculating lymphocytes resulted in a pronounced decrease in delayed hypersensitivity, prolongation of skin-graft survival, selective suppression of humoral antibody responses and additional clinical improvement. Thoracic-duct T cells were depleted slightly more than B cells. There was no effect on responses to induced inflammation. These findings are consistent with the hypothesis that some of the drained cells are essential participants in the inflammatory manifestations of rheumatoid arthritis and systemic lupus erythematosus in these patients.

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HAROLD E. PAULUS, MD:* Many diseases of unknown cause are considered to be autoimmune; most of the rheumatic diseases are included in this category. So-called immunosuppressive drugs have been used with some success in the treatment of various autoimmune diseases,[1-4] but the risk involved in using these cell poisons is high. Moreover, we cannot confidently attribute beneficial effects to a single action of the immunosuppressive drugs because these agents may act on a multiplicity of sites.

According to some reports, thoracic-duct drainage (TDD) has permitted successful cadaver renal transplantation when used as the sole immunosuppressive therapy.[5-7] Its effects on immune responses have also been studied in experimental animals.[8-11]

In this conference we shall discuss the use of thoracic-duct drainage as a tool to study the effects of this method of immunosuppression in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). We shall characterize the general effects of thoracic-duct drainage on various aspects of cell-mediated and humoral immune responses, as well as its effects on induced inflammation. In addition, the effect of thoracic-duct drainage

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ABBREVIATIONS USED IN TEXT
ANA = antinuclear antibody
β_1C = Beta-1-C component of complement
Con A = concanavallin A
DNCB = dinitrochlorobenzene
E-RFC = lymphocytes forming rosettes with sheep red blood cells
HL-A = human leukocyte-locus A
KLH = keyhole-limpet hemocyanin
PHA = phytohemagglutinin
RA = rheumatoid arthritis
SIg = surface membrane immunoglobulin
SLE = systemic lupus erythematosus
SRBC = sheep red blood cells
TDD = thoracic-duct drainage

on the inflammatory manifestations and on some autoimmune markers of systemic lupus erythematosus and rheumatoid arthritis will be presented.

In order to understand thoracic-duct drainage, it is necessary to review the anatomy of lymphocyte circulation (Figure 1). Lymphocytes from the bone marrow and the thymus enter and circulate in the blood. Some lymphocytes migrate through the walls of postcapillary venules directly into lymph nodes. It is presumed that they can also leave the blood and travel through the tissues until they arrive at a lymph node by way of its afferent lymphatics. Antigenic stimulation of lymphocytes may occur in the tissues or in the lymph nodes, and lymphocyte proliferation and recruitment may occur in the nodes. Ultimately many lymphocytes leave the nodes by way of efferent lymphatics, most of which become tributaries of the thoracic duct. The contents of the thoracic duct are then returned to the peripheral blood, and the cycle starts over again. The spleen acts like an intravascular lymph node. Cells leaving the spleen enter the peripheral blood directly, but the rest of the lymphocyte circuit is unidirectional. After a lymphocyte leaves the circulation, it can return only by way of the thoracic duct or by a few of the other major lymphatic vessels. Because the thoracic-duct lymph contains no platelets and very few neutrophils and eosinophils, and has no easily recognizable monocytes, it provides a convenient mechanical separation of lymphocytes from other blood cells.

When we cannulate the thoracic duct, we divert recirculating small lymphocytes and lymphocytes that have been recently antigen-stimulated or newly proliferated, thereby preventing their entry into the bloodstream. This diversion may have immediate effects to the extent that diverted cells are unable to fulfill their function.

A second major effect occurs with prolonged

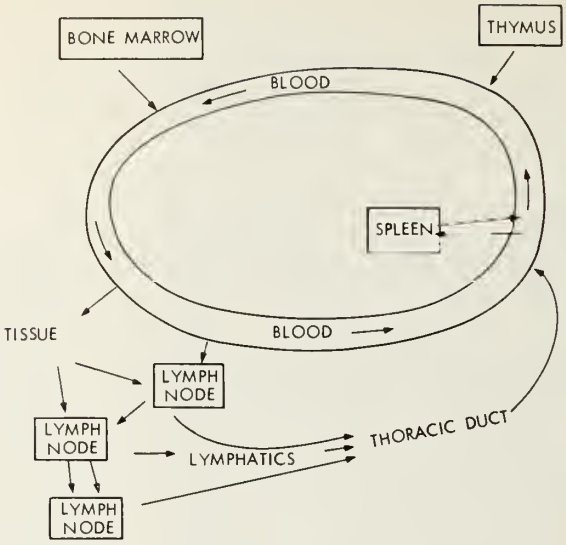

Figure 1.—Anatomy of lymphocyte circulation.

thoracic-duct drainage. If the drained lymphocytes are not returned to the patient, the body's pool of recirculating lymphocytes is gradually depleted, particularly of long-lived (and slowly replaced) recirculating lymphocytes. Therefore, in discussing the effects of thoracic-duct drainage, we shall attempt to distinguish the early effects of lymphocyte *diversion* from the later effects of lymphocyte *depletion*.

Surgical Technique

HERBERT I. MACHLEDER, MD:* The technique of thoracic-duct drainage has been described previously.[12-14] However, premature closure of the fistulae because of technical difficulties has often limited its usefulness both as an investigative tool in the study of autoimmune phenomena and as a therapeutic modality to effect immunosuppression by means of lymphocyte depletion. By carefully modifying several steps in this procedure, it has been possible to prolong the longevity of thoracic-duct fistulae in such a fashion that they can be used in clinical protocols.

The thoracic duct (Figure 2) arises at the cisterna chyli, the confluence of all the infradiaphragmatic lymphatics. It ascends the posterior mediastinum and enters the cervical region in the retroesophageal position. At this point it curves, much as the handle of a cane, goes beneath the left internal jugular vein and unites with a plexus of brachiocephalic lymphatic trunks to form a dilated ampulla at the junction of the left subclavian vein and the left jugular vein. The duct is most accessible for cannulation in this area;

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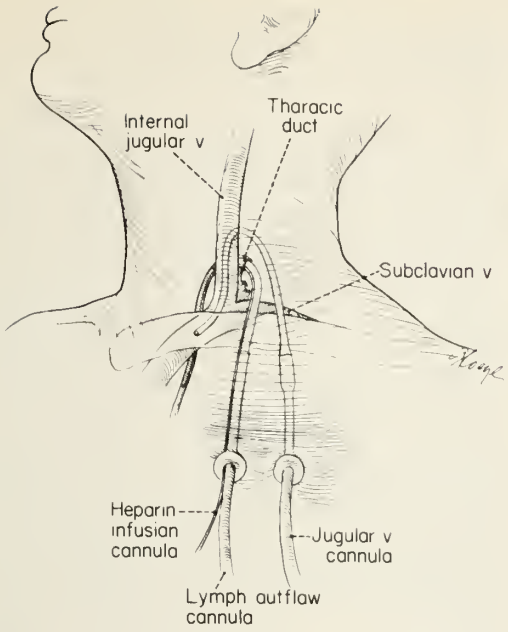

Figure 2.—Surgical anatomy of terminal thoracic duct.

it lies in the scalene anticus fat pad just beneath the clavicular belly of the sternocleidomastoid muscle.

The entire operation is done above the clavicle in the left side of the neck. An incision is made parallel to the clavicle and continued deep to the sternocleidomastoid muscle. After the jugular vein is carefully mobilized, the ampulla is usually easily visible as it enters the jugular subclavian junction. The ampulla is dissected and ligated at its most distal portion; lymph then distends the thoracic duct and the collateral channels that join at this confluence. The collateral channels must be carefully ligated to prevent diversion of lymph from the thoracic-duct fistula, which would otherwise occur after a period of time. We have found that one of the major causes of failure in an initially successful thoracic-duct fistula has been the enlargement of collateral channels that divert the lymph into new lymphovenous communications. If thoracic-duct drainage output begins to fall, retrograde thoracic-duct lymphangiography may show these collateral channels, which can then be ligated, usually under a local anesthetic. The lymph flow then promptly returns to its usual output volume. This drainage problem can be prevented by carefully identifying the collateral channels at the time of the initial operation and checking that they are securely ligated.

After the thoracic duct has been isolated, an incision is made in the duct wall, and probes are

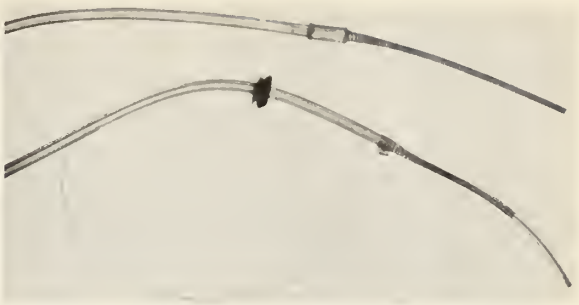

Figure 3.—Components needed for thoracic-duct cannulation. **Bottom:** Soft silastic, double-lumen, wire-wound thoracic-duct cannula; heparin solution is infused through the smaller lumen, and heparinized lymph flows out through the larger lumen. The exit button has been placed on the cannula approximately where the cannula penetrates the skin. **Top:** Soft silastic venous cannula; a valve at the tip of the tube prevents retrograde flow of blood.

passed in a retrograde fashion to disrupt the sets of semilunar valves that line the proximal thoracic duct and prevent regurgitation of blood into the thoracic duct. Unless these valves are carefully disrupted, they will prevent the passage of the soft silastic cannula deep enough into the thoracic duct to establish a secure fistula. The cannulae we have designed (Figure 3) have a double lumen and are made of soft medical-grade silastic. One lumen allows continuous heparin infusion to the tip of the catheter and into the thoracic duct; the second lumen allows free exit of heparinized lymph. A wire coil is embedded in the wall of the cannula and extends from the tip of the tube to include the entire portion that will remain in the subcutaneous tissue. This coil prevents kinking of the tube and obstruction to lymph flow by flexion, extension or head movements that may cause the tube to bend or change its position. In order to maintain a long-term thoracic-duct fistula, it is essential to use a tube that will remain patent but whose composition elicits minimal tissue reaction. Although the very soft medical-grade silastic fulfills the purpose of tissue compatibility, it is easily obstructed. The coiled wire structure within its wall maintains the patency of the tube. The double-lumen tube* is ligated in place in the thoracic duct and is further secured with several other sutures to the scalene fat pad. The tube is then passed through a subcutaneous tunnel over the clavicle and through an exit site in the skin several centimeters inferior to the clavicle. At this point, it exits through a button* consisting of

*Manufactured by Heyer-Shulte Company, Santa Barbara, California.

a porous Teflon pad with a silastic collar. The tube is cemented to this silastic button, which is gradually infiltrated with fibrous tissue in the subcutaneous space, and thus provides a secure point of fixation and a barrier to fluid and bacteria. With this procedure we have been able to maintain cannulae for three months without problems of local sepsis or skin breakdown at the exit site.

A branch of the internal jugular vein is cannulated with a second silastic tube that has a single lumen. This tube is passed through a similar subcutaneous tunnel and is brought out in an infraclavicular position adjacent to the thoracic-duct cannula. This jugular line is used only for the reinfusion of cell-free lymph. The lymph is collected in an iced glass flask set in a movable cart, thereby enabling the patient to be completely ambulatory. Each morning the flask is changed, and the lymph is processed under sterile conditions, using a laminar flow hood and a continuous-flow centrifuge to separate the lymph from the lymphocytes. Cultures of the cell-free lymph are done daily and the lymph is stored under refrigeration until the cultures have been determined to be negative. The lymph is then reinfused through the jugular line from an intravenous pole attached to the movable cart. During drainage, the patient is encouraged to walk; he is able to move about the hospital in a relatively unrestricted fashion for laboratory tests, physical therapy and other requirements.

DR. PAULUS: We have thus established a system for continuous collection of lymph, removal of cells and reinfusion of sterile cell-free lymph that can be continued for many weeks. We have also seen a characteristic time-course of changes occurring during thoracic duct drainage.

Effects of Thoracic-Duct Drainage on Lymphocyte Concentrations and Characteristics

Daily lymphocyte output ranges from 10×10^9 to 50×10^9 early in drainage but decreases as drainage continues, usually stabilizing after three to six weeks at 1×10^9 to 5×10^9. Total lymphocyte output varies with persons and with duration of drainage; the maximum to date has been about 10^{12} cells from a patient whose drainage continued for 102 days. Lymphocyte concentrations in peripheral blood decrease during the first four weeks and then remain at rather low but stable levels. After thoracic-duct drainage, it takes about 15 weeks for the concentration to return to baseline levels. Early in drainage, the cells are almost all small dense lymphocytes. After one to four weeks, larger, lighter cells begin to appear, which often have nucleoli and are sometimes seen in mitotic division.

As the larger cells are less dense, it is convenient to follow their concentrations by discontinuous density gradient centrifugation. When this is done, there has been a progressive decrease in high-density cells associated with an increase in low-density cells during the first eight weeks of thoracic-duct drainage. Surprisingly, there is no evidence of hyperplasia of lymphoid precursors in the bone marrow, although peripheral blood lymphocytes also become larger and less dense.

PHILIP J. CLEMENTS, MD:* In collaboration with Dr. David Yu, we evaluated surface membrane receptors on thoracic-duct lymphocytes and on peripheral blood lymphocytes before and during thoracic-duct drainage. Table 1 shows the results

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TABLE 1.—*Percentages of Lymphocyte Subpopulations as Defined by Various Cell Surface Receptors on Lymphocytes From the Thoracic Duct and the Peripheral Blood of Patients With Severe Rheumatoid Arthritis or Scleroderma**

	Lymphocytes		
	TD†	*PB*	
Cell Surface Receptors	*7 RA and 2 PSS (Percent)*	*11 RA (Percent)*	*11 PSS (Percent)*
Binding sheep red blood cells (T lymphocytes)	60±4	76±3	74±4
Surface Ig (B lymphocytes)			
All Ig classes	24±3	12±2	14±2
IgM only	21±6	10±2	12±2
Binding aggregated IgG (B and L lymphocytes)	27±4	20±2	22±2
Complement receptor (B and L lymphocytes)	29±6	13±1	9±2

PB = peripheral blood; PSS = scleroderma; RA = rheumatoid arthritis; TD = thoracic duct

*All studies were not done in every subject.
†Examined within first 14 days of drainage.

for several membrane receptors as identified on thoracic-duct lymphocytes of nine patients within their first 14 days of drainage. For comparison, the same receptors were evaluated on peripheral-blood lymphocytes from a group of patients with severe rheumatoid arthritis or scleroderma. The values for peripheral blood are not significantly different from those of normal persons previously reported from this laboratory.[15,16]

T lymphocytes were identified by their ability to form spontaneous rosettes with sheep red blood cells (E-RFC), and B lymphocytes were enumerated by immunofluorescent staining of surface membrane immunoglobulin (SIg).[17] Before the staining of surface membrane immunoglobulin with fluorescein-conjugated goat antisera to human immunoglobulin, the cells were incubated at 37°C for 30 to 60 minutes in media free of human serum to induce shedding of any adsorbed or cytophilic immunoglobulin.[18]

Using monospecific fluorescent goat antisera to human immunoglobulins, the IgM class of immunoglobulins accounted for most of the surface membrane immunoglobulin on both thoracic-duct lymphocytes and peripheral blood lymphocytes in this study, as it has in other recent investigations.[19]

By means of an indirect immunofluorescent method, binding of heat-aggregated human IgG was used to identify Fc-receptors (the Fc portion of the antibody molecule) on lymphocytes. By using a combination of immunofluorescent and rosette techniques concurrently, we have been able to identify receptors for aggregated IgG on most B lymphocytes, as well as on a separate population called K or L lymphocytes.[20] Some investigators feel that these lymphocytes may be largely responsible for antibody-dependent cellular cytotoxicity.[18,19,21-23] As K or L lymphocytes do not have surface membrane immunoglobulin and do not rosette with sheep red blood cells, they may represent a subset or grouping distinct from the classical groupings of B and T lymphocytes.[18,19,22,23] Lymphocytes with receptors for the third component of complement were assessed by a rosetting technique using complement-coated zymosan granules.[16] We have found complement receptors primarily on circulating B and L lymphocytes. Only a few circulating T lymphocytes (as assessed by rosetting with sheep red blood cells) also form rosettes with complement-coated zymosan granules.

In several animal systems, T lymphocytes that have become activated or "turned-on" have been shown to develop Fc-receptors.[24,25] It has been suggested that in the autoimmune diseases there may be a greater than normal number of T lymphocytes that have become activated as part of the disease. We therefore searched for such activated T lymphocytes in thoracic-duct lymph and

TABLE 2.—*Receptors for Sheep Red Blood Cells Occurring Simultaneously on Lymphocytes With Receptors for Aggregated IgG or With Surface Immunoglobulin*

Source	Number of Patients	Agg and E-RFC			SIg and E-RFC		
		Total Agg	Total E-RFC	Both Simultaneously	Total SIg	Total E-RFC	Both Simultaneously
Thoracic-duct lymph	3	60.8±15.7	38.7±15.8	4.1±2.1	52.8±15.1	38.4±17.0	2.9±2.2
Blood	9*	19.8± 2.2	73.1± 2.8	3.6±0.6			

Agg = aggregated IgG
E-RFC = lymphocytes forming rosettes with sheep red blood cells
SIg = surface immunoglobulin

*With classical rheumatoid arthritis.

TABLE 3.—*Changes in Absolute Lymphocyte Concentrations and in Percentages of Cells Binding Aggregated IgG or Sheep Red Blood Cells in Lymph and Blood Before and During Thoracic-Duct Drainage*

Drainage Duration	Lymph*			Blood*		
	Lymphocyte Concentration (Per cu mm)	Agg (Percent)	E-RFC (Percent)	Lymphocyte Concentration (Per cu mm)	Agg (Percent)	E-RFC (Percent)
Before drainage	..	..	..	1,690±291	21±2	70±6
Week 1	8,090±1,170	30±6	58±3	1,223±162	..	..
Week 2	6,530±1,350	28±7	62±8	811±142	20±4	..
Week 3	6,500±1,350	30±6	56±3	718± 99	..	..
Week 4	4,500±1,080	38±6	51±4	611±101	24±3	70±7

Agg = aggregated IgG
E-RFC = lymphocytes forming rosettes with sheep red blood cells

*Total number of patients: lymph, 11; blood, 7.

TABLE 4.—*Changes in Absolute Lymphocyte Concentrations and in Percentages of Cells Binding Aggregated IgG or Sheep Red Blood Cells in Lymph During Prolonged Thoracic-Duct Drainage**

Drainage Duration	Lymphocyte Concentration (Per cu mm)	Agg (Percent)	E-RFC (Percent)
Week 1	11,300±1,100	34±11	59± 5
Week 2	7,970± 920	40±13	..
Week 3	7,600±3,290	46±13	48± 8
Week 4	3,130± 670	47±13	44± 6
Week 7	1,330± 280	42±13	48±12
Weeks 12-14 ..	1,670± 780	52± 5	41± 6

Agg = aggregated IgG
E-RFC = lymphocytes forming rosettes with sheep red blood cells

*In three patients drainage continued for up to 14 weeks.

in peripheral blood by assaying lymphocytes simultaneously for binding of aggregated IgG and for binding of sheep red blood cells. The results (Table 2) suggested, however, that only a small percentage of cells from lymph (4.1 percent) or blood (3.6 percent) bound both sheep red blood cells and aggregated IgG simultaneously. Other experiments also showed that cells with surface membrane immunoglobulin were a population of cells different from those that bound sheep red blood cells.

Serial assays from blood and lymph of absolute lymphocyte counts were done and percentages of lymphocytes binding aggregated IgG or sheep red blood cells were calculated during the first four weeks of drainage in 11 patients (Table 3). During drainage, a progressive absolute lymphopenia occurred in both blood and lymph. Moreover, in lymph there was a relative increase in the proportion of B and L lymphocytes, with a reciprocal decrease in T lymphocytes. In blood, however, there was no change in the relative proportions of these two subpopulations.

Three patients were studied for up to 14 weeks of thoracic-duct drainage (Table 4). The previously established trend toward increasing percentages of B and L lymphocytes and decreasing percentages of T lymphocytes continued throughout the thoracic-duct drainage, despite the fact that the absolute lymphocyte count had stabilized by the seventh week. Because of the pronounced lymphopenia, peripheral blood assays were not routinely done after the first month of drainage.

The responses of thoracic-duct lymphocytes to several mitogens were also evaluated serially in three patients by Dr. James B. Peter and Dr. David Yu by methods previously published.[26] The mitogens evaluated included phytohemagglutinin (PHA), pokeweed mitogen, and concanavallin A (Con A). Although the lymphocyte response to mitogens was low in the first few days of thoracic-duct drainage, there was a significant increase in response to mitogens thereafter. This increase was several times greater than the predrainage response of peripheral blood lymphocytes of the patients—or, for that matter, of normal persons. We had anticipated that the response of thoracic-duct lymphocytes to mitogens would have slowly decreased during drainage. Such a decrease in response was seen in the first patient, but in the other two patients in whom drainage continued for up to eight weeks, no such consistent downward trend occurred. We conclude, therefore, that in general there was no consistent change in the level of responses to mitogens during drainage.

Effects of Thoracic-Duct Drainage on Host Immune Responses

Skin Homograft Survival

DR. MACHLEDER: Although there has been extensive documentation of prolonged homograft survival with various immunosuppressive modalities, this study permitted us to determine whether prolongation of homograft survival could be achieved when thoracic-duct lymphocyte depletion was the sole immunosuppressive measure.[27] In seven patients who underwent lymphocyte depletion by prolonged thoracic-duct drainage, full-thickness skin grafts from nonconsanguinous donors were placed in a defect created in the anterior thigh of the patient. These homografts were regularly inspected; and in two cases, where the graft was from a donor of the opposite sex, the chromosomal characteristics of the healed skin graft were verified by biopsy. The survival of the skin homografts varied from 8 to 550 days. The duration of survival did not appear to be correlated with the duration of thoracic-duct drainage or with the number of lymphocytes depleted. A relationship was established, however, between the duration of survival of the skin homograft and the residual lymphocyte output. The residual lymphocyte output represents the extent of lymphocyte depletion and is calculated by dividing the average daily lymphocyte output during the final week of thoracic-duct drainage by the average daily lymphocyte output during the first week of drainage; the result is expressed as a percentage. The patient whose graft survived eight days had a residual lymphocyte output of 80 percent, suggesting that successful depletion of lymphocytes had not been achieved despite 80 days of drainage; a large

number of lymphocytes were still being recovered in the thoracic-duct lymph at the end of thoracic-duct drainage. On the other hand, four patients whose grafts survived between 34 and 550 days had residual lymphocyte outputs of 22 percent or less. The longest surviving graft was in a patient whose residual lymphocyte output was 7 percent.

In one patient in whom the most profound immunosuppression was achieved, it is likely that immunologic tolerance developed to a D matched skin homograft. Two successive skin homografts from the same donor showed prolonged survival with no evidence of rejection. Cytogenic studies of biopsy material from both grafts revealed X-Y male karyotypes of the donor cells. The skin homografts remained intact, although other immune responses (including delayed hypersensitivity skin tests, humoral immune responses and peripheral lymphocyte counts) had returned to normal, and disease activity had reappeared at least six months before the second graft was done. To further assess the patient's immunologic tolerance, a third skin homograft, from a second male donor, was placed on the opposite thigh. The HL-A (human leukocyte-locus A) tissue typing of this graft showed two subloci of incompatibility both with the recipient and the previous donor. Although the skin graft that had been placed during thoracic-duct drainage survived 550 days and a second identical graft placed after return of immunologic competence survived 325 days, the third skin graft was rejected in 14 days. It seems evident that immunologic tolerance developed only to the skin graft that was placed during thoracic-duct drainage. It seems likely that a point is reached during prolonged thoracic-duct drainage when the patient's immunologic competence is considerably attenuated. It remains to be established whether there exists a certain level of immunosuppression at which point predictable and reproducible tolerance to transplanted tissue can be expected.

Delayed Hypersensitivity

DR. PAULUS: We can therefore conclude that skin transplant survival seems to be a function of lymphocyte *depletion,* rather than of thoracic-duct lymphocyte *diversion.* Similarly, delayed hypersensitivity skin test responses to both primary and secondary antigens were diminished after four to six weeks of thoracic-duct drainage. Dinitrochlorobenzene (DNCB) immunization was successful at the end of thoracic-duct drainage in only two of six patients. Intradermal injection of recall antigens produced 15.3 ± 2.3 mm of induration at baseline, but only 2.3 ± 1.5 mm after 32 days of thoracic-duct drainage.

Humoral Immunity

The effect of thoracic-duct drainage on humoral immunity was evaluated in several ways. The primary antigen keyhole-limpet hemocyanin (KLH) was given *at the end* of thoracic-duct drainage. The antibody response[28,29] of the drained patients was comparable with that of 36 control patients with rheumatoid arthritis who were being treated with nonsteroidal anti-inflammatory drugs (Figure 4).

Tetanus toxoid was given as a recall antigen

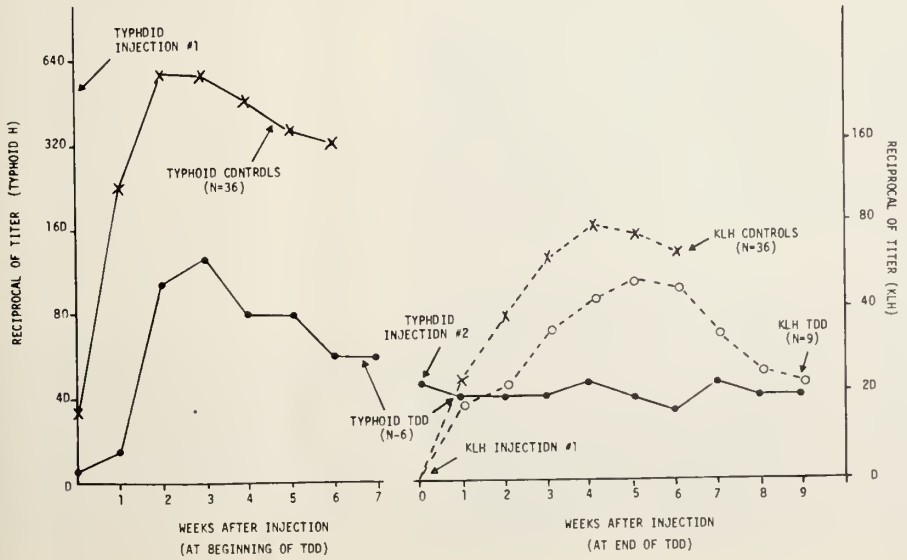

Figure 4.—Antibody responses to the primary antigen keyhole-limpet hemocyanin (KLH) and the recall antigen typhoid H. TDD = thoracic-duct drainage.

both at the beginning and at the end of thoracic-duct drainage; the initial antibody response[30] was similar to that of the controls. The second injection at the end of drainage also increased antibody titer, although the response was not as great as might have been expected.

With typhoid O antigen, there was only a barely perceptible increase in titer after the second injection, given at the end of thoracic-duct drainage, whereas with typhoid H antigen there was no increase (Figure 4).

Immunoglobulins

Serum immunoglobulin concentrations were also studied. During the first week of thoracic-duct drainage, IgG concentration decreased strikingly from 1,450 to 980 mg per dl, with little subsequent change, as compared with concentrations found in control patients with rheumatoid arthritis. Surprisingly, no change in IgM concentration was seen during six weeks of thoracic-duct drainage. IgA concentrations were lower at baseline in the patients undergoing thoracic-duct drainage than in controls with rheumatoid arthritis, and they gradually decreased by about 40 percent during six weeks of drainage. In order to prevent protein depletion in the patients, their cell-free lymph was returned to them daily. Serum albumin remained constant, and the decrease in total protein reflected the changes in immunoglobulin concentrations. Immunoglobulin synthesis rate was examined in one patient by Levy and co-workers.[31] The synthesis of both IgG and IgM was abnormally high before thoracic-duct drainage but was normal when evaluated again at the end of drainage, suggesting that the observed changes in serum concentration are, at least partly, due to decreased synthesis.

Induced Inflammation

Could some of the effects of thoracic-duct drainage be the result of general effects on inflammatory responses rather than of specific effects on immunity? We examined several assays of induced inflammation (Trafuril erythema,[32] microcrystalline sodium urate injections,[33] Rebuck skin windows[34]) before and at the end of thoracic-duct drainage and found no change in them. There was also no effect on marrow granulocyte reserves as measured by etiocholanolone responses[35] or on lymphocyte concentrations in bone-marrow aspirates.

Effects of Thoracic-Duct Drainage on Disease Manifestations

Systemic Lupus Erythematosus

KENNETH NYMAN, MD:* Many of the findings in systemic lupus erythematosus, including cutaneous vasculitis and glomerulonephritis, are thought to be mediated by the deposition of immune complexes. Deposition of immune complexes and complement in blood vessel walls and at the dermal-epidermal junction is found both in lesion tissue and in uninvolved skin of patients with systemic lupus erythematosus.[36,37] The disappearance of immunoglobulin deposits at the dermal-

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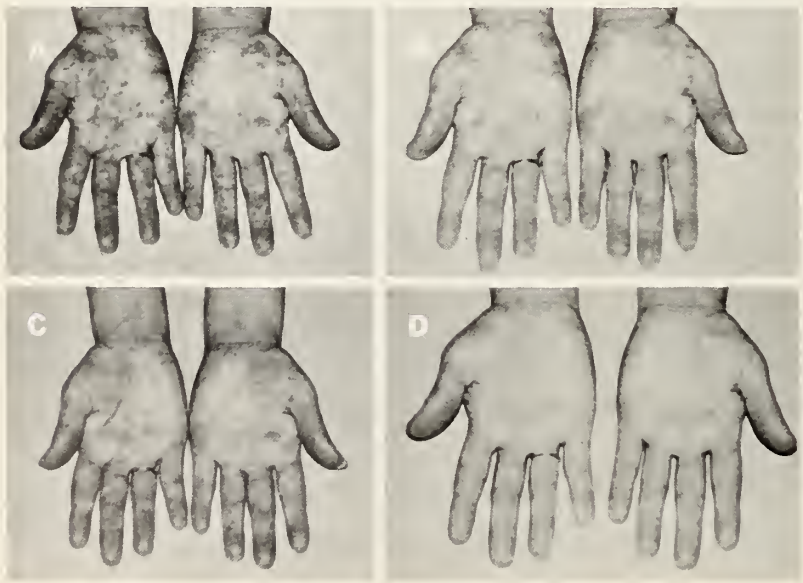

Figure 5.—Serial photographs of patient with systemic lupus erythematosus cutaneous vasculitis. **A:** one week after beginning thoracic-duct drainage; **B:** at end of second week of drainage; **C:** in seventh week; **D:** 11 weeks after end of thoracic-duct drainage.

epidermal junction has been noted in the uninvolved skin of patients with systemic lupus erythematosus treated with cyclophosphamide.[38] It has been suggested that this may serve as a useful indicator of the effectiveness of therapy. As we have stated, prolonged lymphocyte depletion has been shown to produce a significant immunosuppressive effect.

In view of these observations, we decided to study the effects of thoracic-duct drainage, as a noncytotoxic procedure, in a 25-year-old woman with a four-year history of systemic lupus erythematosus manifested primarily by cutaneous vasculitis.[39] She was only partially and intermittently responsive to very high doses of oral corticosteroids and azathioprine. Biopsy studies of skin gave findings consistent with systemic lupus erythematosus. Other manifestations of the patient's disease included lupus nephritis (predominantly membranous), recurrent serositis, pancreatitis, fever, arthralgias and seizures. From September 1974, she had manifested incapacitating vasculitis involving buccal and nasal mucosa, and the skin of face, forearms and hands (including the nails) (Figure 5). Because of failure to control the patient's disease activity with administration of 100 mg of prednisone and 200 mg of azathioprine per day, and because of the recognized dangers and complications associated with long-term oral administration of corticosteroid and azathioprine, we decided to initiate thoracic-duct drainage.

On December 2, 1975, the thoracic duct was surgically cannulated. The volume of lymph in any one 24-hour period ranged from 1,100 to 3,500 ml; the number of lymphocytes drained per day ranged from 200 million cells to 33 billion cells. At the end of ten weeks, 277×10^9 lymphocytes had been drained from the patient.

After one week of thoracic-duct drainage, the patient's condition improved considerably (Figure 5). During drainage, there was no clinical, laboratory or histological evidence of change in the patient's lupus nephritis, and the dosage of prednisone was tapered to 60 mg every other day. She has subsequently been followed as an outpatient, and she was maintained on this amount of prednisone with no evidence of disease activity until July 8, 1976, when a vasculitic lesion was noted on her hard palate. With prolonged drainage the immunoglobulin deposition in the skin decreased.

After ten days of thoracic-duct drainage, examination of skin biopsy specimens showed 3+ continuous fluorescence for β_1C and, after six weeks, 2+ focal deposition. Subsequently, there

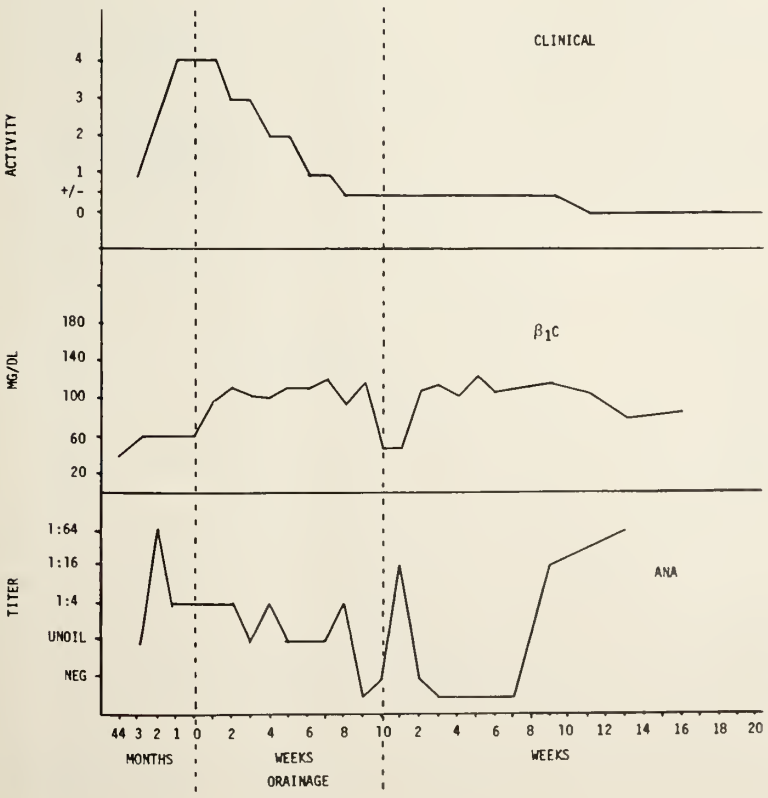

Figure 6.—Clinical activity of cutaneous vasculitis (arbitrary activity scale) and serum concentrations of Beta-1-C (βC) component of complement and antinuclear antibody (ANA) before, during and after thoracic-duct drainage.

were no lesions available for biopsy procedures. Similar distribution and intensity in staining for IgG were present in all specimens. Deposits of IgG and β_1C in uninvolved skin changed from continuous to focal with some decrease in intensity. Staining for IgM did not occur in the lesion or in uninvolved skin. Decreased deposition of IgG and β_1C closely paralleled the clinical course, whereas the antinuclear antibody (ANA) titer did not (Figure 6).

As expected in a patient with active lupus dermatitis, serum β_1C was notably depressed initially, as it had been for four years, in a range from 40 to 60 mg per dl. It rose immediately after initiation of drainage, anticipating the subsequent clinical improvement. By contrast, antinuclear antibody titer did not fall during the first eight weeks of drainage and became negative only at the end of the drainage, when the patient was significantly immunosuppressed.

IgG concentration decreased during thoracic-duct drainage and increased at the cessation of drainage. The results for IgA were surprising; it was undetectable before and early in drainage, but became detectable late in drainage and has since remained so. IgM concentrations fell during drainage, in contrast with the findings in patients with rheumatoid arthritis.

Thoracic-duct drainage was also used as a non-cytotoxic immunosuppressive therapy in a 22-year-old man with systemic lupus erythematosus manifested primarily by proteinuria (10 to 20 grams per day), recurrent superficial thrombophlebitis and cutaneous ulceration. From January 1972, he had been on a regimen of prednisone, 100 mg per day, and azathioprine, 150 mg per day, and had not responded to these drugs. Renal biopsy studies showed proliferative glomerulonephritis. Immunohistologic studies showed positive immunofluorescence in a fine, diffuse pattern for IgG (3+), IgM (2+) and β_1C (4+). On January 2, 1974, the thoracic duct was surgically cannulated. During drainage there was reduction in 24-hour urinary protein loss from 10 to 20 grams per day to 3 to 4 grams per day (Figure 7). During this period, the level of serum protein did not change. In addition, the dosage of oral corticosteroids was tapered from 70 mg of prednisone a day to 55 mg every other day, alternating with 2.5 mg every other day. Findings of postdrainage renal biopsy studies were identical to those of predrainage biopsy studies. In September 1975, aza-

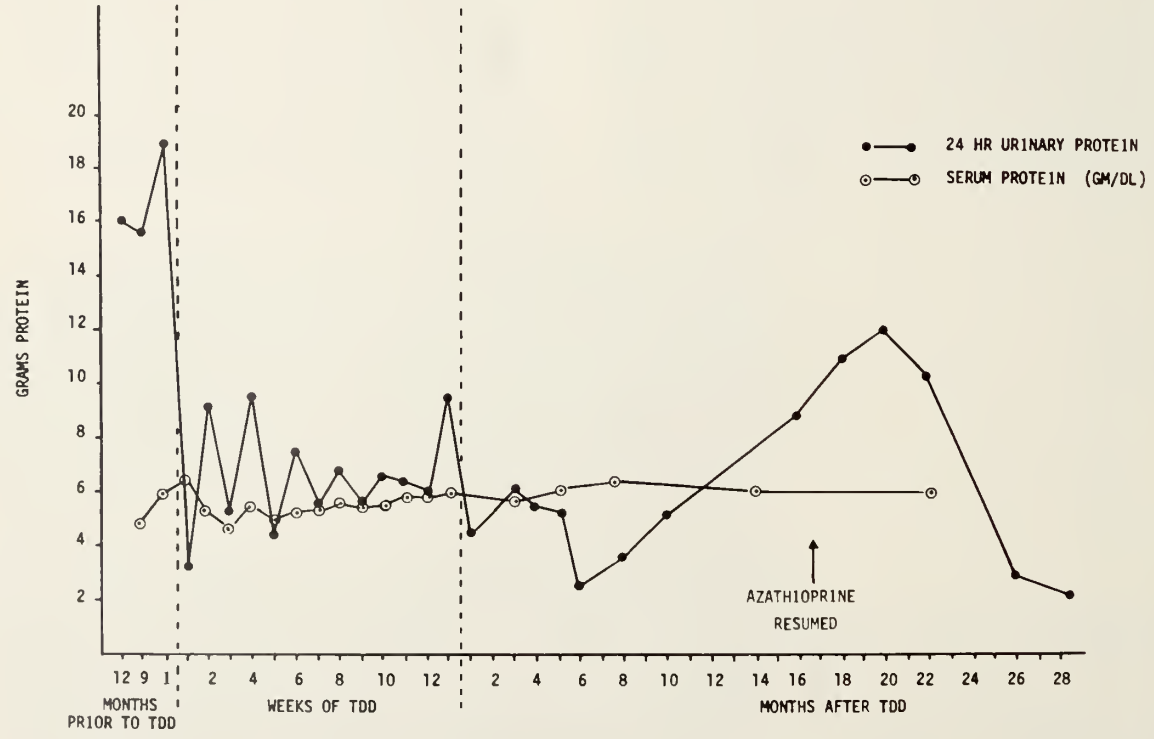

Figure 7.—Urine and serum protein concentrations before, during and after thoracic-duct drainage (TDD) in a patient with systemic lupus erythematosus.

thioprine was started again for decreasing renal function. At present he is receiving azathioprine, 300 mg per day, and prednisone, 50 mg every other day. During thoracic-duct drainage there seems to have been no histologic or immunohistologic change in renal tissue, although there was significant reduction in proteinuria.

The events during thoracic-duct drainage in systemic lupus erythematosus seem to follow this sequence: Initially there is clinical improvement associated with increases in total complement and β_1C; at this time immunosuppression is not present. With further diversion of thoracic-duct lymphocytes, there is a decrease in the deposition of "immune complexes" associated with further clinical improvement and little, if any, immunosuppression. With prolonged drainage, pronounced immunosuppression occurs, as shown by the feasibility of tapering dosages of corticosteroids and the prolonged skin-graft survivals; this is associated with decreasing titers of antinuclear antibody, which eventually become negative.

In summary, there was a prompt anti-inflammatory effect from diversion of thoracic-duct lymphocytes, as manifested by pronounced clinical improvement and rise of complement levels with no evidence of immunosuppression. With prolonged drainage, there was further clinical improvement and decreased "immune complex" deposition in skin; antinuclear antibody became negative; pronounced immunosuppression was shown by prolonged skin-graft viability, and it was possible to reduce corticosteroid doses.

We conclude that some lymphocytes circulating in the thoracic duct are important participants in processes leading to cutaneous vasculitis in systemic lupus erythematosus.

Rheumatoid Arthritis

SEYMOUR LEVINE, MD:* Lymphocytes are thought to play a role in the pathogenesis of chronic inflammatory diseases such as rheumatoid arthritis. They are a prominent component of the infiltrates of inflammatory cells characteristically found in rheumatoid synovium and rheumatoid nodules. In order to study the effects of lymphocyte depletion on the clinical course of rheumatoid arthritis, we removed the lymphocytes circulating in the thoracic-duct lymph through a surgical fistula in nine patients with rheumatoid arthritis.[40]

Studies were done in 12 women with severe dis-

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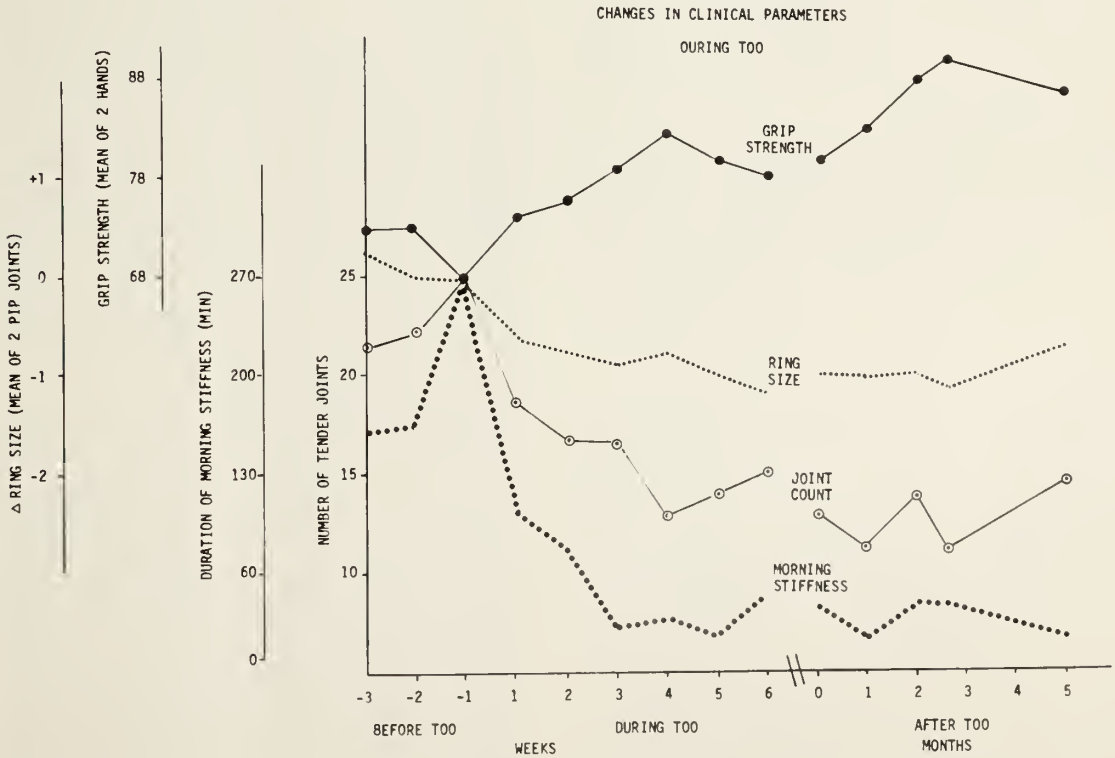

Figure 8.—Mean changes in clinical variables before, during and after thoracic-duct drainage (TDD) in nine patients with rheumatoid arthritis.

abling rheumatoid arthritis. In all there were high titers of rheumatoid factor, and in most patients the tests for antinuclear antibodies were positive; all but one had nodules and most had complicated disease with extraarticular manifestations. The thoracic ducts were successfully cannulated in nine patients and drained for 19 to 105 days (mean 53.4 ± 10.8 days), during which 17×10^{10} to 111×10^{10} (mean $46 \times 10^{10} \pm 12 \times 10^{10}$) lymphocytes were removed. In four patients fistulae were not established successfully, although the patients were subjected to the same general anesthesia and surgical procedures as those in whom cannulation was successful. These four patients were considered to be a comparison group. One patient was included in both groups; an initial attempt at cannulation was unsuccessful, but a second attempt six months later resulted in 105 days of lymph drainage.

Patients were admitted to hospital in the Clinical Research Center at UCLA for at least two weeks before cannulation to permit the patient and the disease to adjust to the hospital environment and to expedite baseline observations. Clinical variables followed each week included counting the number of joints with tenderness or pain on motion; determining maximum grip strength with a sphygmomanometer cuff; measuring the sizes of two preselected proximal interphalangeal joints with jeweler's rings, and recording the duration of morning stiffness.

In most patients administration of all anti-inflammatory drugs, including aspirin, was discontinued two or three days before operation; use of codeine or propoxyphene was permitted as needed for pain relief during drainage. Two patients continued to receive small doses of prednisone, and one patient continued to receive 150 mg of indomethacin per day during drainage.

Subjective improvement in the symptoms of arthritis began within seven days after institution of effective drainage, and measurable objective improvement was noted shortly thereafter. Statistically, significant improvement was noted when various measurements of disease activity were compared with baseline observations (Figure 8). Before drainage, patients' conditions became worse when anti-inflammatory drugs were withdrawn. After establishment of a thoracic-duct fistula, average count of painful joints dropped from 25 to 15 after six weeks of drainage. Similar improvement was seen for morning stiffness, with a drop from more than four hours to 40 minutes; for grip strength, with an increase from 67 to 78 mm of mercury; and for ring size, with a mean decrease of 1.2 units. With reinstitution of therapy with anti-inflammatory drugs, it was noted that improvement in patients' conditions lasted as long as five months after thoracic-duct drainage.

Figure 9.—Decrease in size of rheumatoid nodules in the olecranon bursa and on the extensor surface of the forearm during about five weeks of thoracic-duct drainage. (From Pearson, Paulus, Machleder;[41] reproduced by permission of the New York Academy of Sciences.)

Improvement was only temporary, however, and evidence of active arthritis recurred within 2 to 12 weeks after drainage was discontinued. Nevertheless, in some patients disease activity was less severe and more easily controlled than before the study. The degree of improvement increased during prolonged drainage, and the duration of improvement after drainage seemed to increase with a longer period of drainage. Rheumatoid nodules decreased in size or disappeared during drainage (Figure 9).[41] The erythrocyte sedimentation rate became normal in three patients, but showed little change in the others. Latex titers showed no significant changes.

No improvement occurred after the four unsuccessful attempts at thoracic-duct cannulation, indicating that admission to hospital, anesthesia and surgical therapy were not responsible for the clinical improvement. In the one patient included in both groups, no clinical improvement occurred after unsuccessful cannulation. When successful cannulation was achieved six months later, however, clinical improvement occurred similar to that seen with the other patients in whom drainage was done. This patient's clinical status deteriorated when indomethacin was withdrawn before the initial attempt at cannulation of the thoracic

duct. After the unsuccessful surgical operation and resumption of indomethacin, there was a return to baseline in number of active joints and morning stiffness; however, the patient's condition gradually deteriorated. Six months later cannulation was done successfully and 10^{12} lymphocytes were removed during 105 days of thoracic-duct drainage. Subsequently, prolonged improvement occurred that lasted for nine months after drainage was stopped.

In summary, significant clinical improvement and pronounced suppression of disease activity occurred in nine patients with severe rheumatoid arthritis during prolonged continuous removal of thoracic-duct lymphocytes through a surgical fistula. The reasons for suppression of disease activity are not clear from these studies, nor is the specific role of these lymphocytes in the pathophysiology of the disease delineated by these clinical observations. It is unlikely that lymphocyte depletion affected the underlying cause of the disease, because active arthritis always recurred at some time subsequent to drainage. These findings do, however, suggest that some of the lymphocytes in the thoracic-duct lymph are essential for the continued activity of the inflammation associated with rheumatoid arthritis.

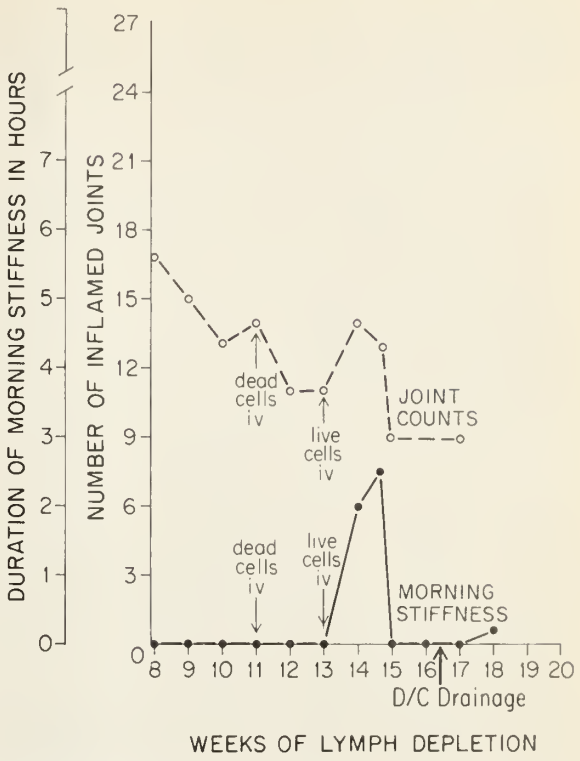

Figure 10.—Exacerbation of morning stiffness and number of inflamed joints after intravenous infusion of 1×10^9 living autologous thoracic-duct lymphocytes during thoracic-duct drainage. Infusion of the same number of dead autologous lymphocytes had no adverse effect.

Lymphocyte reinfusion studies

In order to test this hypothesis, the reinfusion, both intravenously and intraarticularly, of autologous lymphocytes labeled with chromium 51 was studied in four patients.[40] With this method we hoped to assess clinical changes that might be associated with the reinfusion of these lymphocytes as well as to study lymphocyte recirculation.

Intravenous infusion of 1×10^9 autologous ^{51}Cr-labeled live lymphocytes into one patient on day 82 of drainage resulted in a generalized mild exacerbation of arthritis lasting seven to ten days. Such a flare-up did not occur after injection of a similar number of heat-killed cells (Figure 10). A moderate exacerbation of arthritis also occurred with infusion of 1×10^9 live cells into a second patient on day 58 of drainage. No such flare-up occurred when a similar number of live cells were infused into a third patient on day 2 of drainage; however, no improvement in arthritis had yet occurred so soon after thoracic-duct cannulation.

In order to eliminate the technical effects of washing and labeling of the lymphocytes with chromium 51, uncentrifuged whole lymph was reinfused into a fourth patient on three occasions, days 24, 31 and 45 of drainage. Although this patient was informed that lymphocytes would be reinfused at some time, she was totally unaware of the exact days when this was carried out. Exacerbation of arthritis occurred three or four days after cell infusion and was documented by a threefold increase in joint count on two of the three occasions.

Intraarticular injection of 1×10^9 live lymphocytes into the left knee after 15 days of drainage resulted in an acute effusion and persistent inflammation of that joint. An increase in time needed to walk 50 feet from 19 to 29 seconds was associated with the acute inflammation of the knee. On the other hand, no such flare-up occurred when 1×10^9 *dead* cells were injected into the right knee of the same patient on day 21 of drainage.

Distribution of reinfused lymphocytes labeled with chromium 51

After intravenous infusion of labeled living lymphocytes, a tenfold increase of surface gamma counts was noted over the liver and spleen,

whereas much smaller increases occurred over the inflamed knees. Surface counts decreased exponentially during the next four weeks, but the rate of decrease was much slower over the knees than over the liver and spleen.

About 1 percent to 2 percent of the injected radioactivity appeared in the lymph during each day of the first week after injection of live cells. Of this label 40 percent to 50 percent was cell-associated, showing recirculation of labeled lymphocytes from blood to lymph. After injection of heat-killed labeled cells intravenously, no cell-associated radioactivity was found in the lymph. When labeled live lymphocytes were injected into the knee, cell-associated label also appeared in the thoracic-duct lymph. Most of the radioactivity remained in the injected knee, with a small amount detected over the liver or spleen, suggesting that lymphocytes leave the synovial space by way of lymphatics and the thoracic duct, rather than by directly entering the blood.

Finally, autoradiography showed only a few labeled lymphocytes in lymph, blood, synovial fluid and synovium. The slower rate of disappearance of radioactivity from the arthritic knees than from the liver and spleen may show that there is prolonged retention of some lymphocytes in the inflamed joint; control data for normal subjects are not available for comparison.

In summary, these studies showed that lymphocytes labeled with chromium 51 circulate from blood to thoracic duct. The label was widely distributed and could be followed using a gamma counter. Most of the radioactivity went to the liver and to the spleen; relatively little radioactivity went to inflamed joints after intravenous injection. Some labeled cells, however, could be identified in synovium and synovial fluid by autoradiography, indicating perhaps a "homing" mechanism of selected lymphocytes for joints. Some of the lymphocytes injected into a knee joint entered the thoracic duct. Reinfusing live cells intravenously or intraarticularly exacerbated the disease; this did not occur with dead cells. This exacerbation of inflammation further supports a role for some of these lymphocytes in the pathogenesis of rheumatoid arthritis and directly shows a detrimental role of lymphocytes in rheumatoid arthritis.

Summary

DR. PAULUS: To return to our original hypothesis, that we might be able to distinguish effects of thoracic-duct lymphocyte diversion from those of recirculating lymphocyte depletion, we can sum up (Table 5) as follows:

TABLE 5.—*Summary of Effects of Thoracic-Duct Drainage*

Diversion of Thoracic-Duct Lymphocytes
↓ Synovitis in rheumatoid arthritis
↓ Rheumatoid nodules in rheumatoid arthritis
↓ Cutaneous vasculitis in systemic lupus erythematosus
↓ Serum IgG
Depletion of Lymphocytes During Prolonged Thoracic-Duct Drainage
Pronounced ↓ recirculating lymphocyte pool
Pronounced ↓ cell-mediated immunity
Prolonged allograft survival
Selective ↓ humoral immune responses
No effect on induced inflammation
↓ T cells; ↑ B cells

Diversion of thoracic-duct lymphocytes produced a prompt decrease in synovitis and nodule size in rheumatoid arthritis, a diminution of cutaneous vasculitis and proteinuria in systemic lupus erythematosus and a pronounced drop in IgG serum concentrations.

Prolonged thoracic-duct drainage with *depletion* of recirculating lymphocytes was associated with a pronounced decrease in cell-mediated immunity, prolonged skin-graft survival and selective suppression of humoral antibody responses. Thoracic-duct T cells were depleted slightly more than B cells, and there was no effect on responses to induced inflammation. Additional improvement of clinical manifestations also occurred during depletion.

Substantial clinical improvement, although temporary, occurred in these patients with severe rheumatoid arthritis or systemic lupus erythematosus, who had failed to respond to previous therapy. This improvement occurred despite the withdrawal of nonsteroidal anti-inflammatory drugs in the patients with rheumatoid arthritis and the reduction of prednisone doses in the patients with systemic lupus erythematosus. It is consistent with a hypothesis that some of the cells removed from the lymph were essential participants in the inflammatory manifestations of rheumatoid arthritis and systemic lupus erythematosus in these patients. This hypothesis is supported by the exacerbation of inflammation that sometimes occurred three to seven days after we returned the patient's live thoracic-duct lymphocytes intravenously or intraarticularly. The studies using labeling with chromium 51 showed that a few of the reinfused live lymphocytes ended up in in-

flamed synovium and synovial fluid, but they did not show whether these cells play an important part in the inflammatory process. Exacerbation of arthritis occurred fairly soon after drainages of less than four weeks, but remissions were somewhat longer after prolonged depletion; this may show that prolonged depletion temporarily exhausts the supply of a critical subpopulation of lymphocytes, whereas briefer drainage merely diverts these critical cells away from a required pattern of circulation.

Improvement of rheumatoid arthritis during thoracic-duct drainage has been reported by Dumont, Mayer, and Mulholland[42] in one patient; Edgren and associates[43] in two patients; and Wegelius and co-workers[44] in five of six patients. Olhagen and Franksson[45] have reported thoracic-duct drainage in systemic lupus erythematosus. Clinical improvement has also been reported during thoracic-duct drainage of patients with myasthenia gravis,[46,47] multiple sclerosis,[48,49] sympathetic ophthalmia[48] and progressive glomerulonephritis.[50]

Several complications have occurred both in patients in whom drainage was done successfully and in those in whom it was not successful. Septicemia due to contamination of a batch of preservative-free heparin required termination of drainage in our first two patients. A staphylococcal wound infection prevented satisfactory drainage of one of the control patients; she had many vasculitic skin ulcers that were infected with the same organism. Candida vini was found during routine daily cultures of lymph in the patient with lupus cutaneous vasculitis. Although this had not caused symptoms, drainage was stopped and the patient was treated with amphotericin intravenously.

Pleuropericarditis occurred in one patient after four weeks of drainage when synovitis was substantially improved. A similar pleuropericarditis occurred in one of the control patients who was not drained. A platelet count that gradually dropped to 60,000 per cu mm prompted us to stop drainage in one patient. Severe neutropenia that developed slowly in one patient after 70 days of drainage ultimately responded to splenectomy. Splenectomy for the Felty syndrome had also been done in one patient seven years before drainage. In three of the control patients herpes zoster later developed, and in three other patients hemorrhagic cystitis occurred in association with cyclophosphamide therapy.

Weighing the risks against the benefits, we think that most of our patients have benefited from thoracic-duct drainage and the careful medical management that they received. However, we do not recommend the routine application of this procedure for the treatment of severe rheumatoid arthritis or systemic lupus erythematosus; thoracic-duct drainage is a relatively complex and mechanically demanding procedure that requires scrupulous attention to detail by the nursing and technical team during a long, expensive hospital stay. If cytotoxic drugs are not given shortly after the end of thoracic-duct drainage, the effects on both immune responses and disease manifestations are only temporary. Nevertheless, thoracic-duct drainage provides a useful quantitative tool for studying the effects of lymphocyte diversion and depletion on various manifestations of presumably autoimmune diseases. It may give us insight into the pathogenesis of some of these diseases. It provides clinical justification for *in vitro* and animal investigations of lymphocyte function and suggests that drugs that specifically affect lymphocyte function may be useful in these diseases.

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Specialty Conference

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Nonobstructive and Obstructive Hypertrophic Cardiomyopathies

JOHN ROSS, JR., MD:* *The major purpose of this clinical conference on hypertrophic cardiomyopathy, with its expression both in nonobstructive and obstructive forms, is to direct attention toward current diagnostic and management approaches to this now commonly recognized type of heart disease. As we shall hear from Dr. Shabetai, this disorder has been recognized only for about 15 years, and within that time it has provoked much controversy from the standpoint of nomenclature, as well as its pathophysiology. However, the position of hypertrophic cardiomyopathy in the spectrum of cardiac diseases is now relatively well understood. Moreover, it is now appreciated that this condition can mimic other cardiac disorders, including coronary heart disease, valvular heart disease (mitral stenosis, mitral regurgitation, congenital and acquired aortic stenosis), papillary muscle dysfunction and the mitral valve prolapse syndromes, congenital heart disease, and other forms of primary and secondary myocardial disease. Hypertrophic cardiomyopathy is sufficiently common to be encountered from time to time in everyday clinical practice, particularly if the diagnosis is kept in mind and searched for, and its recognition is important because of unique features of the clinical course and the responses to various forms of therapy.*

Our first discussant will be Dr. Ralph Shabetai,

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ABBREVIATIONS USED IN TEXT

ASH = asymmetrical septal hypertrophy
HCM = hypertrophic cardiomyopathy
HOCM = hypertrophic obstructive cardiomyopathy
IHSS = idiopathic hypertrophic subaortic stenosis
SAM = systolic anterior motion

who will review the history of hypertrophic cardiomyopathy.

RALPH SHABETAI, MD:† In 1957 Sir Russell Brock,[1] cardiac surgeon at Guys Hospital, London, opened the door to the present era of interest in the hypertrophic cardiomyopathies when he described the case of a patient referred to him for aortic valvotomy. In the patient all the appropriate studies then in vogue for the diagnosis of aortic valve stenosis had been done, including measurement of a systolic pressure gradient between the left ventricle and the brachial artery—both obtained by direct needle punctures. At operation Brock found a normal aortic valve and observed massive hypertrophy of the interventricular septum. He ascribed this finding to previous hypertension and drew the analogy with infundibular stenosis of the right ventricular outflow tract which may develop as a secondary phenomenon in patients with ventricular septal defect and severe pulmonary hypertension, or which may be unmasked after the surgical relief of severe pulmonary valve stenosis.

In 1958 Donald Teare,[2] pathologist at St. Thomas' Hospital Medical School, London, reported on nine cases observed over six years in a paper entitled "Asymmetrical Hypertrophy of the Heart in Young Adults." Dr. Teare described patients with systolic murmurs and one with a diastolic murmur which resembled that of mitral stenosis so closely that the patient had been referred for mitral valvotomy. From his paper it is clear he recognized that the upper portion of the interventricular septum is predominantly involved, that the disease may involve both ventricles, that it disturbs the function of the mitral valve, that it is familial in nature and that it is characterized by disordered myofibrils. Dr. William Roberts has traced the history of the hypertrophic cardiomyopathies to the 19th century when the 1869 volume of the *Gazette Medicale de Paris* contained articles by Liouville and by Hallopeau,[3] each describing a patient with what now would be called hypertrophic obstructive cardiomyopathy (HOCM), but credit for the first unequivocal description of this disorder and for opening the whole investigational question of asymmetrical hypertrophy appears to belong to Dr. Teare.

Over the ensuing years clinical, surgical and pathological reports rapidly accumulated. At first the major emphasis was upon the means of distinguishing between aortic valve stenosis and HOCM; a 1960 paper by Goodwin,[4] a leading authority in the field of the cardiomyopathies, includes a table containing three columns devoted to this differentiation. To Dr. Braunwald and his colleagues[5,6] then working at the National Heart Institute, we owe the concept of variable dynamic obstruction to left ventricular outflow and the term idiopathic hypertrophic subaortic stenosis (IHSS). This concept was also developed by Dr. Goodwin and his associates in England,[7] Dr. Wigle[8] in Canada and other investigators working in several countries. These studies emphasized the importance of physiological and pharmacological interventions that alter cardiac size, cardiac contractility and peripheral vascular resistance on the systolic murmur and pressure gradient in reaching an accurate diagnosis. In general, the cardiological community concluded that Teare's asymmetrical hypertrophy of the heart, Brock's functional obstruction to left ventricular outflow and Braunwald's IHSS were one and the same disease.

Throughout the 1960's, the mechanisms responsible for and the clinical importance of the systolic pressure gradient between left ventricular outflow tract and the remainder of the left ventricle, and the development of surgical treatment, attracted much attention. Considerable controversy developed between those who believed that the systolic pressure gradient was caused by true obstruction, and those who believed that these pressure gradients were caused by cavity obliteration or even entrapment of the catheter tip within the interstices of the left ventricle.[8-10] In 1966 Ross and associates presented angiographic and hemodynamic evidence that obstruction is caused by an abnormal position of the mitral valve in the left ventricular outflow tract during systole.[9] But lingering doubts persisted because crucial questions remained unanswered; were obstruction and nonobstructive hypertrophic cardiomyopathy different disorders or merely variable manifestations of the same disorder, and could one evolve into

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the other? What were the relative roles of asymmetrical hypertrophy of the septum and abnormal motion of the mitral valve?

Subsequently, echocardiographic studies appeared in 1969,[11] and gradually a picture of the global and regional abnormalities of left ventricular anatomy and function was put together which allowed a proper assessment of the prevalence of the hypertrophic cardiomyopathies, and provided a tool for family studies. On the other hand, indiscriminant echocardiography of inferior quality resulted in an alarming number of incorrect diagnoses of IHSS. Improvements in echocardiographic techniques and resolution, as well as two dimensional echocardiography, have gone a long way toward solving this problem, but in their wake they have posed some new questions. We now know that asymmetrical septal hypertrophy, or ASH as it was later dubbed,[12] may occur in conditions other than hypertrophic cardiomyopathy, and that hypertrophic cardiomyopathy may be symmetrical. Moreover, hypertrophic cardiomyopathy may occasionally be obstructive when it is symmetrical, and systolic anterior motion of the mitral valve may be seen on echocardiograms of patients without hypertrophic obstructive cardiomyopathy.[13,14]

As early as 1960, Goodwin[4] was emphasizing that HOCM is a generalized myocardial disorder which may cause inflow as well as outflow obstruction, and that the major problem causing difficulties for most of the symptomatic patients may be reduced ventricular diastolic compliance. In 1967 we reported the cases of three patients who had been referred for mitral valvotomy because of apical diastolic murmurs and signs of obstruction to left ventricular inflow.[15] These cases serve to remind us that not all cases of hypertrophic cardiomyopathy simulate aortic stenosis, a fact recognized by Teare,[2] one of whose patients died following exploration of the mitral valve for "mitral stenosis."

The therapeutic history of these disorders is no less fascinating than that of its clinical features. Studies on effects of pharmacological interventions on the clinical and hemodynamic features of the hypertrophic obstructive cardiomyopathies suggested that therapy with beta-adrenergic blocking agents should be beneficial, though whether from reduction of systolic outflow pressure gradient, from heart rate effects or from increased ventricular diastolic compliance remains an unanswered question, as does the relevance of effects due to

Figure 1.—The initial terminology crisis.

acute intravenous administration to those due to long-term oral therapy. Surgical treatment has been practiced since shortly after the concept of dynamic left ventricular outflow obstruction was established. The surgical procedures have progressed from simple incisions in the outflow tract to excision of variable quantities of ventricular septal myocardium, and replacement of the mitral valve has even been employed. Satisfactory symptomatic relief and reduction of ventricular systolic pressure gradients have been reported, but clear evidence that the operation protects from sudden death remains to be obtained.

As many as 20 different names have been applied to hypertrophic obstructive cardiomyopathy depending upon the anatomic, pathophysiological, surgical, hemodynamic, familial and echocardiographic features. To this day the English have preferred HOCM and the Americans IHSS (Figure 1), but the echocardiographers and radionuclear physicians may turn them both to "ASH and dust."

DR. ROSS: *The contributions that have been made by the application of echocardiography, cardiac catheterization and angiography to the hypertrophic cardiomyopathies have been of paramount importance in our ability to comprehend and diagnose the various hypertrophic cardiomyopa-*

TABLE 1.—*Congenital Problems Occasionally Associated With Hypertrophic Cardiomyopathy*[33]

Friedreich ataxia
Lentiginosis
Noonan syndrome
Glycogen storage disease
Children of diabetic mothers
Secundum type atrial septal defect
Ventricular septal defect
Persistent ductus
Pulmonary valve stenosis
Aortic stenosis

thies. However, thoughtful correlation of certain laboratory and clinical findings has made it possible to recognize hypertrophic cardiomyopathy at the bedside. Dr. Guy Curtis will review the clinical presentation of this disorder.

GUY CURTIS, MD, PHD:* Hypertrophic cardiomyopathy (HCM) is not rare but the true incidence in the general population is unknown. Many patients, particularly those without symptoms and physicial findings, never come to medical attention.[16] The condition may be discovered at any age, and occasionally in races other than Caucasian.[8,17-19]

Genetic Patterns

Before the use of echocardiography, the disease was thought to occur in 30 percent to 40 percent of patients as an autosomal dominant trait, the remaining cases being termed sporadic.[8,19,20] Patients in whom the diagnosis could be confirmed by hemodynamic studies were most frequently male (male/female ratio, 1.5:1 or greater), but females predominated in the group over age 60 years. When detected by echocardiography as asymmetric septal hypertrophy (ASH), Epstein and his associates studying the families of patients in 30 consecutive cases of ASH[16] concluded, from findings in more than 100 first degree relatives, that the disorder (1) is genetically transmitted as an autosomal dominant trait in the families of most patients afflicted with clinically evident HCM, (2) seldom occurs sporadically, (3) afflicts males and females with equal frequency and (4) has a greater incidence in the population than previously appreciated because ASH is not clinically evident in most patients. There was a lower prevalence of ASH in children of affected families, and it is possible that localized septal abnormality may exist without significant septal hypertrophy but become manifest later in life.[16]

ASH has been described in association with the congenital diseases listed in Table 1. Friedreich ataxia is the most frequently associated condition; in as many as 33 percent of patients with this condition there is echocardiographic evidence of ASH.[27]

Presenting Symptoms

The older the patient when first examined, the more severe the presenting symptoms are likely to be. A family history of heart disease and sudden death may be elicited. Dyspnea or excessive fatigue on extertion is the most common initial complaint with other presenting symptoms, in decreasing frequency of occurrence, being chest pain, palpitation, lightheadedness and syncope.[22-28]

Chest pressure or pain is a common early symptom and may resemble angina pectoris due to coronary artery disease, although in some patients the pain is atypical and episodes may be prolonged. In as many as 20 percent of patients with ASH and HCM over 45 years of age, there are either significant coronary artery lesions or coronary artery anomalies that could account for angina pectoris.[24,25] The chest pain tends to respond poorly to administration of nitroglycerin.[24,29]

Palpitation may be present in up to half of symptomatic patients.[25] Serious ventricular tachyarrhythmias or bradyarrhythmias have not been documented with normal daily activity in most of these patients, and there is no clear evidence that those having such dysrhythmias are at greater risk for sudden death than patients without palpitation. Atrial fibrillation is poorly tolerated, often leading to emergency room admission because of the sudden onset of low cardiac output and acute pulmonary edema.[30] Many of the serious systemic thromboembolic events reported in patients with HCM have been associated with this rhythm.

Syncope is relatively common in patients with HCM (20 percent to 30 percent) and may be the only compaint, occasionally being quite disabling. The occurrence of syncope does not appear to bear a relation to the pressure gradient in the left ventricular outflow tract, and it does not necessarily carry an ominous prognostic significance. Lightheadedness often occurs on suddenly assuming the erect position, immediately after exercise or during exercise.

Orthopnea, paroxysmal nocturnal dyspnea and ankle edema are infrequent presenting symptoms.

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These symptoms usually accompany long-standing disease and hence are more commonly found in older patients. However, circumstances which produce acute deterioration in left ventricular performance, such as atrial fibrillation, can provoke these symptoms.

Physical Findings

The jugular venous pressure usually is not elevated, but the A wave may be accentuated. The carotid pulse rises rapidly and, when obstruction is present, it may be bifid. The carotid pulse abnormalities may be accentuated, and the bifid nature of the carotid pulse appreciated, only when the patient rapidly assumes the erect position or during postextrasystolic beats.[6,22]

The apical impulse is usually thrusting in character, with presystolic lift; a triple apical impulse can sometimes be appreciated, consisting of a presystolic lift followed by two systolic expansions, the second one occurring in late systole. The presence of a systolic thrill, a triple apical impulse and bifid carotid pulse are highly correlated with significant left ventricular outflow obstruction. The thrill is localized most frequently to the apex and along the lower left sternal border. Frank and Braunwald[28] have reported that the average peak systolic pressure gradient in patients with thrills was 74 mm of mercury, but the thrill alone was not always reliable in predicting significant obstruction, nor did it correlate with the degree of functional impairment.

The first and second heart sounds may be normal, and a single second sound or paradoxical splitting of S2 usually are correlated with significant outflow tract obstruction. Systolic sounds of low to medium frequency which correlate with the end of systolic anterior motion (SAM) and the peak of the carotid pulse have been recorded in patients with HOCM and termed "pseudoejection sounds."[31] They are thought to emanate from the mitral apparatus. Occasionally, high pitched systolic sounds similar to ejection clicks have been found with significant hemodynamic obstruction. A fourth heart sound can be heard in most patients.

The characteristic systolic murmur of HCM is variable in intensity and heard best along the lower left sternal border or at the apex. It is ejection in character, beginning after the first sound, and of medium pitch. Without certain maneuvers, soft murmurs may be difficult to distinguish from functional ejection murmurs. The murmur is often longer at the apex, a finding which may relate to associated mitral regurgitation.[34] Murmurs of grade 3 or greater intensity tend to be associated with left ventricular outflow obstruction. The murmur may be heard in the axilla, but it seldom radiates to the carotid arteries. A short, low pitched early to mid-diastolic murmur is heard at the apex in approximately 5 percent of patients with HCM[32] and may represent filling sounds or abnormal mitral valve movement during ventricular filling, or both.

TABLE 2.—*Effects of Interventions on Murmur Intensity and Duration*

Increase	*Decrease*
Standing	Squatting
Valsalva maneuver	Handgrip
Amyl nitrite	Phenylephrine infusion
Postpremature ventricular contraction beat	Elevating the legs when supine
Isoproterenol infusion	

The response of the murmur to maneuvers is very helpful in making a bedside diagnosis (Table 2). Generally, interventions that decrease end-diastolic left ventricular size, increase myocardial contractility and reduce the distending pressure in the outflow tract increase the intensity and duration of the murmur (for example, standing or the Valsalva maneuver). Obverse effects decrease the murmur (for example, squatting or phenylephrine infusion, Table 2).[6,35] Rarely, the Valsalva maneuver may produce paradoxical attenuation of the murmur when there is very severe disease due to pronounced outflow tract obstruction and notably reduced flow.

Clinical Course

Variability is the hallmark of the clinical course in patients with HCM, and the risk of sudden death seems unrelated to clinical disability or hemodynamic findings.[25,26,28] Asymptomatic or mildly disabled patients have a greater tendency to remain stable. More seriously disabled patients have a more varied course, characterized by progressive disability, congestive heart failure and death, and fewer patients remain stable or improve. Deterioration may be associated with the onset of atrial fibrillation or ventricular ectopy, syncope or disabling angina pectoris. In a minority of patients with HCM the heart eventually dilates, obstructive features disappear, and the clinical features of congestive heart failure, responsive to conventional therapy and aggravated by propranolol administration, may emerge. Retrospective studies in

seriously disabled patients[25] indicate that they were asymptomatic with a murmur at a mean age of 20 years, symptomatic at mean age of 30 years and disabled by symptoms at mean age of 35 years. There is no good evidence at present that medical therapy alters the course of the disease. Infective endocarditis occurs in a small percentage of patients and antibiotic prophylaxis is therefore recommended for dental and surgical procedures.

Sudden death is estimated to occur at a rate of approximately 4 percent per year, and it is presumed to be secondary to arrhythmias. Asymptomatic as well as symptomatic patients are at risk for this complication, as are patients with the entire spectrum of hemodynamic findings. Men with a family history of sudden death seem to be at the highest risk. There is no evidence that medical therapy with propranolol alters the incidence of sudden death; surgical therapy may alter the outlook, but consideration of this form of treatment must be weighed against a relatively high operative mortality in some series.[17]

Electrocardiography

DR. ROSS: *In hypertrophic cardiomyopathy there is frequently hypertrophy of all the cardiac chambers, but the involvement is greatest in the left ventricle. Selective septal hypertrophy often results in electrocardiographic patterns of left ventricular hypertrophy which differ from those of concentric left ventricular hypertrophy, as found in association with hypertension or aortic valvular stenosis. Various forms of accelerated atrioventricular conduction also have been described in patients with hypertrophic cardiomyopathy, and in their families; some have classic Wolf-Parkinson-White patterns and others have variants. Dr. Engler will review some of these electrocardiographic features of* HCM.

ROBERT L. ENGLER, MD:* Using the criteria of Romhilt and Estes,[36] which are quite specific but not highly sensitive, left ventricular hypertrophy generally has been found in about a third of patients who have asymmetrical septal hypertrophy; the voltage criteria of Sokolow[37] also are met in about a third of these patients. In patients with HCM and a systolic pressure gradient, electrocardiographic evidence of left ventricular hypertrophy is more common,[5] but the association between left ventricular hypertrophy and the presence or absence of a pressure gradient is not sufficiently close to be clinically reliable. Idiopathic familial electrocardiographic left ventricular hypertrophy is often associated with left ventricular hypertrophy.[9]

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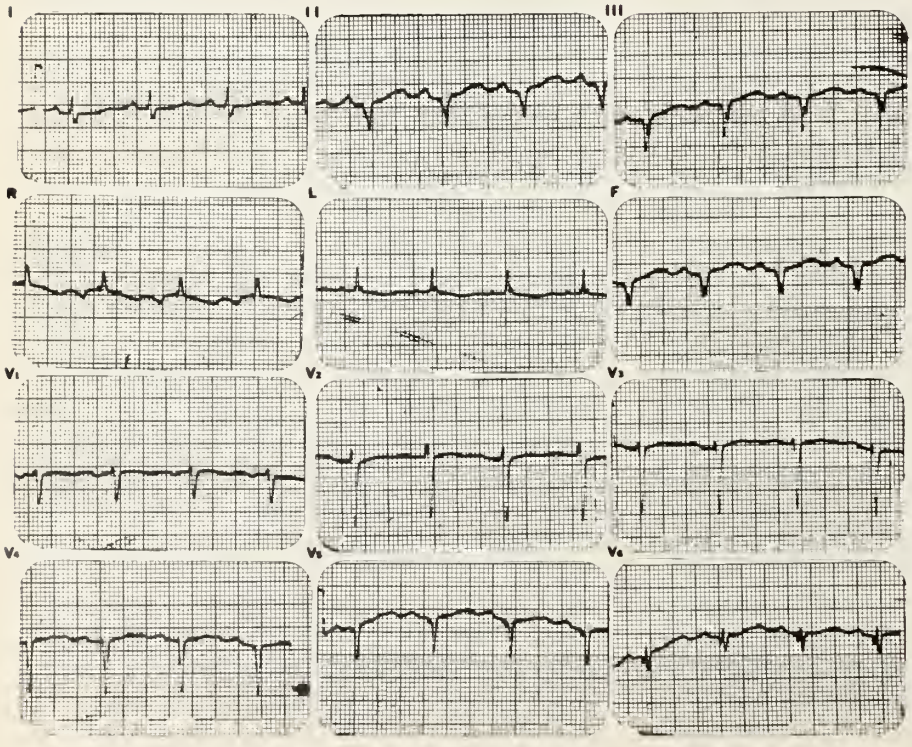

Figure 2.—This electrocardiogram in a 35-year-old woman shows significant Q waves in the inferior and anterior precordial leads. Typical asymmetric septal hypertrophy was present on echocardiography. Cardiac catheterization showed normal coronary arteries and a subvalvular gradient only after a premature ventricular depolarization, and during the strain phase of the Valsalva maneuver.

We have recently carried out studies in 44 patients with asymmetric septal hypertrophy recognized by echocardiography.[38] A variety of left ventricular and left atrial hypertrophy patterns was found. The incidence of left ventricular hypertrophy was 33 percent. In comparing our patients having asymmetrical septal hypertrophy with patients having aortic valvular stenosis, two electrocardiographic patterns of left ventricular hypertrophy tended to be associated with HCM: small Q waves in leads V_4-V_6, and an R/S ratio in V_1 greater than 0.2 (Figure 2). Among our patients with valvular aortic stenosis and left ventricular hypertrophy, we found none with Q waves in V_4, and an R/S ratio in V_1 exceeding 0.2 was not observed.[38] Both of these electrocardiographic findings can be useful when evaluating patients with systolic murmurs.

"Pseudoinfarction" patterns are common in patients with HCM, and Q waves are recorded in about a fourth of patients. However, one must keep in mind, especially when dealing with older persons, that HCM and coronary atherosclerosis may coexist; under these circumstances the Q waves could represent true myocardial infarction. The location of the Q waves does not help in differentiating true infarction from pseudoinfarction patterns; anterior, inferior or lateral Q waves may appear in patients who have HCM and normal coronary arteries. A clue to the identification of the Q waves of HCM may be found in the T wave; QS or QR complexes in HCM are almost invariably associated with upright T waves; therefore, T wave inversion strongly suggests accompanying ischemic heart disease.[39] Occasionally, Q waves regress in patients with HCM,[39] and Q waves may appear or disappear in cases that progress from nonobstructive to obstructive cardiomyopathy.[15,40] The Q wave also may appear or disappear following surgical myectomy of the interventricular septum. The abnormal Q waves in patients with hypertrophic obstructive cardiomyopathy, and in their relatives, often are striking in appearance; they may not be broad, but they are often of considerable amplitude, sometimes 10 to 15 mm or more.

Left atrial enlargement, by the criteria of negative P wave area in lead V_1 exceeding 0.04 mm per second or P wave duration in lead II exceeding 0.11 mm per second, is found in a fourth to a half of patients with HCM.[38,40,41] Atrial hypertrophy does not correlate with any particular clinical features, and there is not a close correlation between electrocardiographic and echocardiographic measures of left atrial enlargement.[42]

We have observed a variety of nonspecific ST segment and T wave changes in hypertrophic cardiomyopathy, usually ST segment depression and T wave flatting or inversion, but these are not helpful in differential diagnosis.

The Wolf-Parkinson-White syndrome and delta waves without PR interval shortening are more common in persons with HCM than in the general population, but they are seen in a minority of patients with HCM.[46] We did not find any examples in our analysis of 44 patients with echocardiographic evidence of asymmetric septal hypertrophy. Wolf-Parkinson-White patterns in the settings of asymmetrical hypertrophy may be found in patients with overt HCM, as well as in their relatives. The QTc may be prolonged in patients with asymmetric septal hypertrophy.[38]

In summary, in patients with HCM there may be electrocardiographic evidence of left ventricular hypertrophy, left atrial hypertrophy is frequent and there may be abnormal Q waves and nonspecific repolarization changes. Left ventricular hypertrophy is more common in obstructive forms of HCM. In a patient with a systolic murmur, an R/S ratio greater than 0.2 in lead V_1 or a Q wave in V_4, electrocardiographic evidence of left ventricular hypertrophy should suggest the possibility of HCM. When "pseudoinfarction" Q waves are present in HCM, T wave discordance is the rule.

Echocardiography

DR. SHABETAI: In the evolution of our understanding of HCM, echocardiography has been of inestimable value. Indeed, in this condition echocardiography often realizes its potential for obviating the need for invasive studies. In HCM the structural abnormalities that have been identified on echocardiograms include a greatly increased thickness of the interventricular septum, lesser increase in the thickness of the left ventricular posterior basal wall, a normal or reduced left ventricular end-diastolic dimension and an abnormal anterior position of the mitral valve. The functional abnormalities include systolic anterior motion (SAM) of the superior leaflet of the mitral valve, decreased E to F slope of the mitral valve, presumably reflecting reduced ventricular compliance, mid-systolic closure of the aortic valve, decreased systolic thickening of the interventricular septum and increased systolic thickening of the posterior left ventricular wall. In

keeping the concept of the dynamic nature of this disorder, the functional features may be exaggerated or induced by physiologic and pharmacologic maneuvers that decrease cardiac size and increase cardiac contractility.

When all the echocardiographic abnormalities described above are recorded on an echocardiogram, the diagnosis of hypertrophic obstructive cardiomyopathy can be made with certainty. However, when only part of this echocardiographic spectrum is found, plaguing questions remain. For instance, how great must be the disproportion between the thickness of the posterior wall and the ventricular wall before asymmetrical septal hypertrophy is diagnosed, and how specific for idiopathic cardiomyopathy is the echocardiographic finding of asymmetrical septal hypertrophy? We also need to know the pathophysiologic mechanism of systolic anterior motion of the mitral valve in hypertrophic obstructive cardiomyopathy. When we have answered that question, we need to know how commonly systolic anterior motion of the mitral valve is found in patients who do not have hypertrophic cardiomyopathy and what mechanism results in this mitral valve motion abnormality in such patients. The echocardiographic features of HCM will be discussed by Dr. Dennis Costello.

DENNIS L. COSTELLO, MD:* As emphasized earlier in this conference, obstructive cardiomyopathy represents only a subgroup of the hypertrophic cardiomyopathies. In the era when cardiac catheterization and left ventriculography were the sole available means for definitive diagnosis, symptomatic patients with HCM and obstruction generally were the ones identified. Those patients having obstruction only upon provocation, and those with nonobstructive hypertrophy, were less likely to be identified. The development of echocardiography yielded a much more sensitive, noninvasive means of detecting the entire spectrum of hypertrophic cardiomyopathies,[11,43,44] and the ability to screen large numbers of asymptomatic patients[45] has further substantiated the prevalence of the familial form of the disorder.

In 1969 echocardiography was first used to show characteristic abnormalities of the interventricular septum in the hypertrophic cardiomyopathies.[46] Substantial hypertrophy of the ventricular septum with less hypertrophy of the left ventricular posterior basal wall was suggested to be the pathognomonic anatomic abnormality in many forms of obstructive and nonobstructive HCM.[12] This asymmetric septal hypertrophy (ASH) can be diagnosed only when the anterior and posterior septal margins can be clearly demarcated and the septum is at least 1.3 times as thick as the posterior basal free wall.[12] In clearcut cases of ASH, the septum to free wall ratio exceeds 1.5 and the septum also contracts poorly. This combination of abnormalities usually signifies the presence of idiopathic myocardial disease, but rare instances of left ventricular hypertrophy secondary to hypertension or aortic stenosis also have been reported to have ASH.[47] This observation may reflect the fortuitous concurrence of two separate abnormalities in the same patient, or asymmetric hypertrophy may develop in response to pressure load on the left ventricle in some persons.

Although echocardiograms are highly sensitive and relatively specific in the diagnosis of ASH, certain important pitfalls must be avoided. Technically inadequate delineation of the anterior and posterior margins of the septum is by far the most common cause of an incorrect diagnosis. Also, disproportionate thickening of the right (or anterior) portion of the septum occurs in right ventricular hypertrophy secondary to pulmonic stenosis or severe pulmonary hypertension.[48] This increase in septal thickness should not be mistaken for that of HCM. In addition, posterior basal myocardial infarction with resultant posterior wall thinning in a concentrically hypertrophied ventricle may result in ASH. On the other hand, in most patients with hypertrophic cardiomyopathy there is echocardiographic evidence of ASH, although rarely the hypertrophy can be symmetrical; necropsy studies in the latter patients have reported cellular changes in the ventricular free wall similar to those frequently seen in the septum of the genetically transmitted form of ASH.[49] This finding suggests that a subgroup of hypertrophic cardiomyopathies may exist in which the pathologic abnormality is diffuse and does not selectively involve the interventricular septum. In addition, recent hemodynamic data have suggested that the hemodynamic abnormalities of HCM with obstruction may rarely occur in patients without ASH.[14]

Angiographic studies have suggested that the subvalvular systolic pressure gradient results largely from apposition of the anterior mitral

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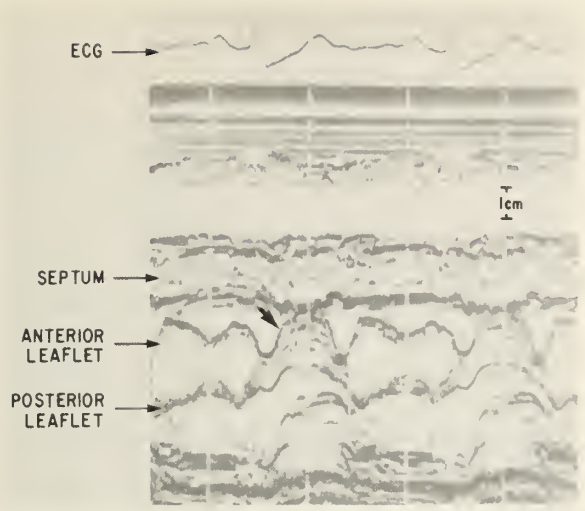

Figure 3.—Echocardiogram and electrocardiogram (ECG) in a patient with hypertrophic cardiomyopathy. The thickened interventricular septum contracts poorly and is asymmetrically hypertrophied. The anterior leaflet of the mitral valve shows systolic anterior motion **(arrow)** and decreased E to F slope in diastole. Reproduced by permission of the publisher and the author from Gosink BB: Exercises in Diagnostic Radiology—Diagnostic Ultrasound, Vol 8. Philadelphia, W.B. Saunders Co, 1976.

leaflet against the hypertrophied interventricular septum in systole.[9,50] Shah and co-workers[11] first illustrated by echocardiography the systolic anterior motion (SAM) of the anterior leaflet of the mitral valve in a patient with HCM and an outflow systolic pressure gradient (Figure 3). Extensive SAM is a characteristic feature when significant outflow obstruction is present, and maneuvers such as the Valsalva maneuver or administration of amyl nitrite, which increase the systolic pressure gradient, also increase the amplitude and duration of concurrently-recorded SAM. The absence of SAM in a technically satisfactory echocardiogram makes the diagnosis of *obstructive* HCM questionable, but the presence of SAM is not pathognomonic of obstruction. Moreover, instances of mild SAM have been noted in nonobstructive hypertrophic cardiomyopathy, hypovolemia, aortic regurgitation and severe mitral valve prolapse.[13,51] The phenomenon of pseudo-SAM, associated with exaggerated posterior wall motion, is now well recognized.

Since SAM is present or can be induced in patients with obstructive cardiomyopathy, Henry and co-workers have attempted to quantitate the extent of subvalvular obstruction from echocardiograms.[52] They theorized that the severity of the obstruction is related to the extent and duration of SAM and computed an index of obstruction by dividing the time during which the outflow tract is narrowed by the mean septum-anterior mitral leaflet separation during systole. This value was compared with the actual pressure gradient and a regression equation was developed. Other investigators have suggested that the gradient computed by this means does not correlate well with the gradient determined by cardiac catheterization.[53]

In addition to SAM, diastolic abnormalities of mitral valve motion are commonly present. Decreased diastolic closing velocity (E to F slope) is common in all forms of hypertrophic cardiomyopathy.[43] This finding is nonspecific and represents slowed atrial emptying (and slowed left ventricular filling) secondary to decreased left ventricular compliance.[54]

The constellation of ASH, SAM, decreased E to F slope of the mitral valve, and normal or reduced end-diastolic dimension (Figure 3), serves to differentiate hypertrophic cardiomyopathies from other forms of valvular or myocardial disease. Occasionally, confusion may occur in studies in elderly patients with valvular aortic stenosis because echocardiographic features similar to those in HCM without ASH may be present. The ventricle is hypertrophied, end-diastolic dimension may be reduced and the E to F slope is diminished in both instances. However, in valvular aortic stenosis, the aortic root is dilated and dense echoes from the region of the thickened, fibrotic and often calcified aortic valve are noted. The presence of thin aortic valve leaflets with normal early systolic opening in hypertrophic cardiomyopathy virtually excludes the diagnosis of valvular aortic stenosis in adults. In addition, mid-systolic closure with secondary opening of the aortic valve is commonly observed in HCM. Most likely, this closure represents mid-systolic increase in outflow obstruction with decreased aortic blood flow. This finding also can be seen in discrete subvalvular aortic stenosis.[55]

Echocardiograms also are extremely useful in differentiating HCM from other forms of cardiomyopathy. The thickened poorly contracting septum and the normal or reduced systolic and diastolic ventricular dimensions distinguish HCM from the dilated ventricle of congestive cardiomyopathy (Figure 3). In restrictive cardiomyopathy, the ventricular dimensions may be similar to those in HCM; however, in the former the hypertrophy is symmetrical and less pronounced, and the ampli-

tude of septal systolic excursion is normal, or only mildly and not selectively reduced.

Echocardiography may be utilized to follow serially the effects of medical or surgical treatment of HCM. Reduction in the extent and duration of SAM following propranolol therapy has been reported on a few occasions.[43] A study carried out in patients 6 to 12 months after surgical myectomy showed reduction in the amplitude and duration of SAM associated with a decrease in the systolic pressure gradient;[56] however, septal and posterior wall thicknesses were not reduced 6 to 12 months after relief of the outflow tract obstruction. Also, the closing velocity of the mitral valve did not increase following myectomy, reflecting the persistence of diminished left ventricular compliance following surgical intervention.

Differential Diagnosis

DR. ROSS: *The problem of reaching a precise diagnosis has been hindered somewhat by the many, and often changing, classifications of* HCM. *However, the various features of both the obstructive and nonobstructive forms are now well enough established that a diagnosis can be made by noninvasive techniques. Dr. Martin LeWinter will discuss the differential diagnosis.*

MARTIN M. LEWINTER, MD:* When physical signs such as arterial pulsus bisferiens, a sustained, hyperdynamic left ventricular impulse and a systolic murmur that behaves in a typical fashion during maneuvers are present, the diagnosis of hypertrophic cardiomyopathy with dynamic subvalvular obstruction can be made at the bedside with reasonable certainty. However, when physical findings are atypical or when obstruction is mild, present only with provocation or consistently absent, a bedside diagnosis is often difficult. My discussion will center around problems in differential diagnosis which may be encountered across the entire spectrum of hypertrophic cardiomyopathy, both with and without obstruction.

Probably the most common diagnostic problem is the differentiation of HCM from fixed valvular aortic stenosis. Symptomatically, valvular aortic stenosis and hypertrophic cardiomyopathy share a number of features. In both, patients may present with chest pain, dyspnea, or syncope and, in both, there may be a long history of a heart murmur. One feature which may be helpful is that in valvular aortic stenosis, it is unusual for symptoms to occur before age 40 (except in congenital forms), whereas this occurrence is not at all unusual in HCM. Usually results of physical examination can conclusively differentiate HCM from valvular aortic stenosis. In patients with HCM and outflow obstruction at rest, the rapid rising (often bisferiens) arterial pulse and the behavior of the systolic murmur during maneuvers is in pronounced contrast to the findings in valvular stenosis. For example, while in both entities the murmur becomes louder in the beat following an extrasystole, the Valsalva maneuver and amyl nitrite increase the intensity of the murmur of HCM (Table 2) but diminish the murmur of valvular aortic stenosis. Confusion may occasionally arise in an elderly patient with significant valvular stenosis who has arterial pulses that may not be slow rising, due to age-related vascular changes. Auscultation of an associated aortic regurgitation murmur suggests that one is dealing with valvular rather than subvalvular obstruction.

When hypertrophic cardiomyopathy occurs without a murmur at rest, the question of fixed valvular obstruction is, of course, no longer pertinent. In the occasional case in which hypertrophic cardiomyopathy with obstruction is not readily distinguishable at the bedside from valvular obstruction, several noninvasive tests may be helpful. Although typical electrocardiographic changes of left ventricular hypertrophy are common to both disorders, the finding of notably abnormal initial forces is suggestive of hypertrophic cardiomyopathy.[57] Radiographic findings of aortic valve calcification and poststenotic dilatation, or a squaring off of the left cardiac border due to pronounced septal hypertrophy in HCM are helpful differential points. It should be emphasized that cardiac fluoroscopy is far more sensitive than routine radiography of the chest in detecting aortic valve calcification and should be employed in patients in whom problems in differential diagnosis exist. As discussed by Dr. Costello, echocardiography is an exceedingly useful tool in differentiating fixed valvular obstruction from hypertrophic obstructive cardiomyopathy. The presence or absence of thickened aortic valve leaflets on echocardiography is also a helpful differential point, and while many patients have thickened aortic valve leaflets without hemodynamically significant obstruction, normal-appearing aortic leaflets on echocardiography virtually exclude valvular obstruction. Finally, the systolic time intervals and

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external carotid pulse recordings may be helpful adjuncts in distinguishing between these two disorders. Prolongation of the left ventricular ejection time of postpremature beats has also been suggested as a sensitive sign of obstructive hypertrophic cardiomyopathy.[58]

Mitral valve prolapse may occasionally mimic HCM in several respects. Chest pain and dyspnea are common complaints in symptomatic patients with mitral prolapse and, like hypertrophic cardiomyopathy, prolapse is often familial. On physical examination, the characteristic arterial pulse abnormalities of HCM with obstruction are not present in mitral valve prolapse, nor is there evidence of left ventricular hypertrophy. However, the classical mid-systolic to late systolic click of mitral valve prolapse may occasionally be mimicked by systolic sounds of uncertain origin occurring in patients with hypertrophic cardiomyopathy.[31] Perhaps the most confusing differential point between mitral prolapse and HCM with obstruction is in distinguishing between the behavior of the systolic murmur. The careful use of bedside maneuvers will generally serve to make this distinction. During the Valsalva maneuver, the murmur of mitral prolapse generally becomes longer in duration but not louder, while the murmur of HCM with obstruction increases in intensity. Isometric handgrip exercise generally results in a decrease in the intensity of the murmur of hypertrophic cardiomyopathy, while that of mitral prolapse usually increases. Both murmurs may decrease during squatting. In some patients, however, the mitral valve prolapse murmur shortens during squatting but does not disappear, and occasionally it may increase in intensity. During postpremature beats, the murmur of HCM with obstruction increases in intensity, whereas that of mitral prolapse usually decreases in intensity and tends to occur later in systole. Although cases of patients with combined mitral prolapse and hypertrophic cardiomyopathy have been reported, the significance of this association is uncertain.

The frequent association of á variety of musculoskeletal abnormalities, many of which are features of the Marfan syndrome, may occasionally be helpful clues in pointing to the presence of mitral prolapse in patients with a murmur that is difficult to assess. Findings on a radiograph of the chest are almost always normal in cases of the mitral valve prolapse syndrome (except in unusual cases in which mitral regurgitation is severe), so that radiographic features that suggest HCM aid in the differential diagnosis.[59] An electrocardiogram in patients with mitral valve prolapse is usually normal, but may show a repolarization pattern suggestive of "posteroinferior ischemia"; mitral valve prolapse occasionally is associated with abnormal inferior Q waves, a pattern which may also be seen in hypertrophic cardiomyopathy.[57] As in most differential diagnostic problems relating to HCM, echocardiography is probably the single most useful noninvasive test to distinguish mitral prolapse from hypertrophic cardiomyopathy. Asymmetric left ventricular hypertrophy and systolic anterior motion of the mitral valve are not echocardiographic features of mitral prolapse, whereas in most patients with mitral prolapse the diagnosis can be confirmed by the typical posterior motion of mitral valve during systole.[59]

The presence of a flail mitral leaflet due to ruptured chordae tendinae (usually causing severe mitral regurgitation) constitutes a special problem, which at the bedside may resemble HCM with obstruction. Patients with flail mitral leaflet, particularly when seen early in the course of illness, may have a small amplitude, rapidly rising (but not bisferiens) arterial pulse; a hyperdynamic but not sustained left ventricular impulse, and a loud ejection quality systolic murmur. The murmur behaves like the murmur of mitral regurgitation during maneuvers, despite the diamond-shaped ejection character. Therefore, careful use of the Valsalva maneuver, squatting and administration of amyl nitrite are useful distinguishing features because the murmur of a flail mitral leaflet behaves in an opposite fashion to that of HCM with obstruction (Table 2). In addition, unlike patients with hypertrophic cardiomyopathy, patients with flail mitral leaflet commonly have a history consistent with the acute onset of pulmonary congestion. In doubtful cases, echocardiography is once again of great utility in differentiating flail mitral leaflet from hypertrophic cardiomyopathy. Cases of chronic isolated mitral regurgitation occasionally are mistaken for HCM, but can be distinguished by most of the same differential features useful for distinguishing a flail leaflet.

In occasional patients with hypertrophic cardiomyopathy, problems in diastolic filling may dominate the clinical and hemodynamic features. In such patients, features may be noted on physical examination that mimic mitral stenosis, including diastolic rumbles and sounds resembling opening snaps.[15] These findings may be related to an

element of functional inflow obstruction as a result of notably reduced diastolic compliance and possibly abnormal mitral valve motion, although only modest mitral valve gradients have been documented in such patients during cardiac catheterization. Classification of such patients within the HCM spectrum requires the identification of other features of this disorder. This is easily accomplished in patients with coexistent outflow obstruction, since the systolic murmur behaves in the typical fashion, and typical echocardiographic features are present. When outflow obstruction is not present, major left ventricular hypertrophy and particularly asymmetric septal hypertrophy remain very useful diagnostic features. While reduced diastolic compliance may result in a decrease in the echocardiographic EF slope of the anterior mitral leaflet, other echocardiographic features of mitral stenosis are absent in these patients. Restrictive cardiomyopathy is a term that should be reserved for use in patients whose clinical presentation mimics constrictive pericarditis and who do not have massive hypertrophy; therefore, HCM is not considered an example of restrictive cardiomyopathy in spite of the compliance fault.[60]

It should be pointed out that the presence in a patient of mild degrees of asymmetric septal hypertrophy, unassociated with systolic anterior motion, must be viewed with caution; such patients should probably not be categorized as having HCM until all other known causes of this finding have been excluded and the significance of this echocardiographic abnormality is better understood.

The so called "hyperkinetic heart syndrome" may mimic HCM. The former is a relatively poorly defined syndrome in which findings suggestive of adrenergic hyperactivity are present without identifiable cause. At the bedside, the patients sometimes have tachycardia and often have systolic hypertension and bounding pulses. On cardiac examination, a hyperdynamic precordium and systolic flow murmur may be found. Whether or not such patients have, or can develop, organic heart disease is not clear. However, these patients share with hypertrophic cardiomyopathy patients an element of systolic hyperfunction, and it has been suggested that in some instances this syndrome may be a precursor.[61] Cases of the hyperkinetic heart syndrome should be readily distinguished from HCM by the presence in the patient of a murmur which does not behave in a fashion typical of dynamic subvalvular obstruction, the absence of pulsus bisferiens and the absence of ASH. However, in an occasional patient features common to both disorders, including SAM, may seem to be present.

Hemodynamic Studies

DR. ROSS: *Hemodynamic and angiographic studies are still required in some patients to clarify diagnosis and in others when surgical treatment is under consideration. Dr. Allen Johnson will discuss the hemodynamic features of* HCM.

ALLEN D. JOHNSON, MD:* A discussion of the hemodynamic abnormalities encountered in the various hypertrophic cardiomyopathies must take into account recent information that challenges the concept of a unifying anatomic or hemodynamic profile[16] common to all the hypertrophic cardiomyopathies. For example, the controversy surrounding the systolic pressure gradient encountered in patients with asymmetric septal hypertrophy and "obstruction" now must be extended, because echocardiographically documented systolic anterior motion of the anterior mitral leaflet and the hemodynamic features of intraventricular obstruction both can occur without asymmetric septal hypertrophy.[62,63]

Late in the natural history of some patients with hypertrophic cardiomyopathy, left ventricular contractile performance may become significantly depressed,[7] but the major focus of my remarks will be directed towards the hemodynamic derangements which are commonly encountered in patients with HCM. The important hemodynamic abnormalities fall into four categories: (1) hyperdynamic or exaggerated left ventricular contraction, (2) a systolic pressure gradient between the body of the left ventricle and the outflow tract which represents dynamic obstruction to ejection of blood from the ventricle, (3) malfunction of the mitral valve apparatus with associated mitral regurgitation and (4) increased diastolic stiffness of the left ventricular chamber.

Also it is common to record a small systolic pressure gradient in the right ventricular outflow tract, presumably related to the hypertrophied septum. Any or all of these hemodynamic abnormalities may occur in a given patient with or without anatomically documented ASH; consequently, hemodynamic data must be interpreted

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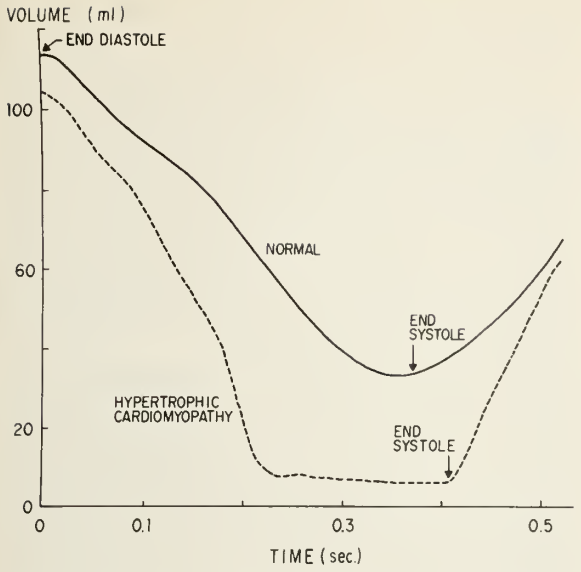

Figure 4.—Time course of ventricular volume during a single cardiac cycle in a normal subject and a patient with hypertrophic cardiomyopathy. Note in the latter the reduced end-diastolic volume and the rapid and sustained ventricular emptying.

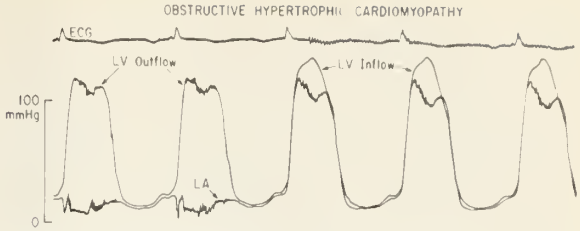

Figure 5.—Pressure tracings from equisensitive catheter tip micromanometers from a patient with obstructive hypertrophic cardiomyopathy and asymmetric septal hypertrophy. In the first two complexes, one catheter is in the left atrium and the other just below the aortic valve. In the remaining complexes, the catheter previously positioned in the left atrium has been advanced just across the mitral valve to the inflow region of the left ventricle; a pressure difference between the left ventricular inflow and outflow area is now apparent. Note the bifid character of the left ventricular pressure pulse in the outflow tract. ECG = electrocardiogram, LA = left atrium, LV = left ventricle.

in the context of the abnormalities identified by echocardiography or angiocardiography.

The various hypertrophic cardiomyopathies have in common hyperdynamic contraction of the left ventricle. The ejection fraction is increased and often exceeds 80 percent, and the rate of ejection, when normalized for end-diastolic volume, is remarkably augmented when compared with that in normal patients. It appears that patients with obstructive as well as those with nonobstructive HCM share this feature of near completion of ejection in the first half of systole. The phenomenon of rapid and complete early ejection is illustrated in Figure 4. No ejection takes place in late systole—an apparent sustained or near "isometric" contraction of the left ventricle, which is commonly reflected as left ventricular "cavity obliteration" noted on cine-left ventriculography.[10,64]

The second important hemodynamic abnormality is the systolic pressure gradient between the body or inflow portion and the outflow area of the left ventricle (Figure 5). Previously it was considered that spontaneous or provocable systolic pressure gradients were limited to patients with asymmetric septal hypertrophy. However, several recent studies have described an intraventricular systolic pressure gradient in patients without evidence for asymmetric septal hypertrophy, but in whom concentric left ventricular hypertrophy and exaggerated left ventricular contraction were present.[13,65] Since the original descriptions of idiopathic obstructive hypertrophic cardiomyopathy, there has been considerable controversy regarding the significance and proper hemodynamic interpretation of the systolic pressure gradient.[8-10] It can easily be appreciated that a catheter in the body of a hypercontractile left ventricle could be trapped within the obliterated cavity of the left ventricle during systole and could therefore measure a pressure not arising within the true left ventricular cavity. "Catheter entrapment" is commonly encountered during the course of cardiac catheterization in patients with hypertrophic cardiomyopathy, and can lead to the faulty impression that one is dealing with a true pressure gradient between the body and the outflow region of the left ventricle. Careful study is necessary to show conclusively that the measured systolic pressure gradient does not represent catheter entrapment artifact; this can be accomplished by transseptal catheterization of the left ventricle[9] so that the catheter may be withdrawn from the left ventricular apex, or advanced from the left atrium, into the region just in front of the mitral valve (the inflow tract), where the catheter is presumed to be lying free within the left ventricular body and therefore not entrapped (Figure 5). Alternatively, a catheter passed retrogradely through the aortic valve can be carefully positioned in front of the mitral valve, in the inflow tract of the left ventricle. When proper care is taken during recording of the pressure within the

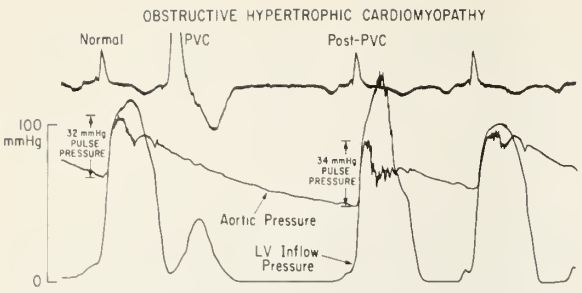

Figure 6.—Catheter-tip micromanometers recording left ventricular and aortic pressures in the same patient as Figure 5. Following a premature ventricular contraction (PVC), the systolic pressure gradient between the left ventricle (LV) and the aorta increases, but the aortic pulse pressure fails to increase significantly.

free left ventricular cavity, compelling evidence favoring a true systolic pressure gradient in many patients with asymmetric septal hypertrophy can be assembled (see Figure 5).[8,9]

As the systolic murmur in classical obstructive HCM increases with maneuvers that decrease end-diastolic volume or increase the rate of left ventricular emptying, so will the measured systolic pressure gradient; the gradient increases or appears during the strain phase of the Valsalva maneuver; during administration of isoproterenol, nitroglycerin or nitroprusside, and in the cycle following a premature ventricular contraction. A decrease or an increase of less than 5 mm of mercury in the arterial pulse pressure (Figure 6) during the cycle following a premature ventricular contraction—the Brockenbrough response—was previously thought to be limited to patients with asymmetric septal hypertrophy accompanied by a systolic intraventricular pressure gradient, but this response has now been documented in the absence of ASH and also in the absence of a spontaneous or provocable systolic pressure gradient.[64]

Dysfunction of the mitral valve apparatus with consequent mitral regurgitation is the third important hemodynamic abnormality which can occur in patients with HCM. At the time of left ventricular angiography, patients with classical obstructive hypertrophic cardiomyopathy uniformly have some degree of mitral regurgitation, and in general patients with more severe obstruction tend to have more severe mitral regurgitation.[7,34] Often the mitral regurgitation is not hemodynamically important, and prominent V waves in the left atrial or pulmonary wedge pressures are not observed. Occasionally patients with HCM have severe mitral regurgitation, the degree of which may vary with induced changes in the systolic pressure gradient.

A Venturi effect caused by rapid blood velocity near the anterior mitral leaflet has been postulated as a possible mechanism for causing the anterior mitral leaflet to remain open during rapid ventricular ejection.[16] Alternatively, malposition of the papillary muscles may be responsible for the mitral leaflet malposition.[9,50] Both mechanisms could provoke obstruction to left ventricular outflow and mitral regurgitation.

Left ventricular distensibility is usually reduced in patients with hypertrophic cardiomyopathy.[7,66] In fact, decreased left ventricular compliance may be the dominant factor responsible for symptoms of pulmonary congestion.[7] In patients with asymmetric septal hypertrophy, as well as those with concentric hypertrophy, there commonly are increased left ventricular end-diastolic pressures associated with normal or reduced end-diastolic volumes. In these patients, small increases in end-diastolic volume may give rise to significant elevations in end-diastolic pressure despite normal systolic function. Furthermore, limitation of end-diastolic volume by the hypertrophied left ventricular myocardium may limit the Frank-Starling mechanism as regulator of cardiac function. It is important to recognize that these abnormalities of *diastolic* left ventricular function are not accompanied by decreased systolic performance; the increased left ventricular filling pressure is secondary to myocardial hypertrophy, not to myocardial failure.

DR. ROSS: *It is important to emphasize that in patients with obstructive* HCM, *because of the dynamic nature of the obstruction the pressure gradient tends to develop progressively during the course of each cardiac systole. There is no obstruction initially, leading to the sharp, early arterial upstroke, but the arterial pulse falls rapidly as the obstruction develops. The pressure gradient may also be variable over time, and can be altered by a variety of interventions, as Dr. Johnson has discussed. For example, the clinically useful Valsalva maneuver or assumption of the upright posture both produce a decrease in venous return, a fall in arterial pressure and reflex tachycardia, all of which reduce ventricular volume and the caliber of the outflow tract. The secondary reflex increase in contractility further augments the degree of obstruction with these maneuvers,*

and the pressure gradient across the outflow tract increases.

Radiographic Findings

We have come to recognize that the angiographic features of HCM *can be quite characteristic, and Dr. Charles Higgins will describe both the findings on a plain roentgenogram and the angiographic anatomy in this condition.*

CHARLES B. HIGGINS, MD:* Findings on a plain x-ray film of the chest frequently are normal and usually are nonspecific in patients with HCM. Pulmonary venous hypertension, manifested radiographically by reversal of the vertical gradation in diameter of pulmonary vessels, and signs of pulmonary edema are observed in the minority of patients. In a subgroup of patients there is an unusually high degree of resistance to left ventricular filling and consequently there may be findings that mimic the pulmonary findings in mitral stenosis.[15] On occasion the appearance of signs of interstitial pulmonary edema (Kerley B lines) or alveolar edema are related to the onset of atrial fibrillation.

Fluoroscopic examination in hypertrophic cardiomyopathy shows vigorous movement of the left ventricular borders. In contradistinction to the findings in valvular aortic stenosis, systolic expansion of the ascending aorta is not exaggerated.

The cardiothoracic ratio on frontal thoracic radiographs is normal (<0.50) in approximately half of patients with documented subaortic gradients.[6,7] In a group of 64 patients in the early report of Braunwald and co-workers, the cardiothoracic ratio ranged from 0.40 to 0.67 and there was no correlation of this ratio with peak systolic gradient, functional classification or eventual prognosis. Many patients do show radiographic evidence of left ventricular enlargement, and localized convexity has been observed on the upper aspect of the left ventricular border in a minority of patients. The latter sign is purported to relate to hypertrophy of the upper portion of the interventricular septum and contributes to a square cardiac contour in some instances. A substantial degree of cardiomegaly and left ventricular enlargement has been observed in those patients with significant mitral regurgitation.

The left atrium is enlarged in many patients but usually to a relatively lesser extent than the left ventricle. Greater degrees of atrial enlargement are observed in the presence of mitral regurgitation or atrial fibrillation, and in patients in functional class IV.[6] In a small subgroup of patients radiographic findings simulate mitral stenosis with pulmonary venous hypertension, pronounced left atrial enlargement and no left ventricular enlargement.[15] Right-sided chamber enlargement has been unusual in adult patients with this disease.

The aorta is not usually dilated in hypertrophic cardiomyopathies, as it is in most patients with valvular aortic stenosis and in nearly half of patients with discrete fixed subvalvular aortic stenosis. In older patients with HCM, prominence of the ascending aorta may be observed as a consequence of incidental systemic hypertension, or due to buckling of the aorta when the aortic valve position is altered by ventricular enlargement.

A left ventriculogram in HCM shows abnormalities of structure and function in systole and to a lesser extent during diastole.[6,9,50,67] It has been suggested that left ventricular filling is restricted or prolonged; however, detailed analyses of cineangiograms of patients with hypertrophic cardiomyopathy have not confirmed abnormal reduction in average left ventricular filling rate,[68] although little filling may occur during diastasis. The diastolic volume is normal, or in some instances less than average.[67] The normal or reduced end-diastolic volume contrasts with the increased volume observed in congestive cardiomyopathy.

The left ventricular wall thickness is usually increased to a greater degree than in valvular aortic stenosis. This, combined with decreased cavity size, results in a ratio of cavity to wall thickness which is below the normal range and lower than in most patients with aortic stenosis.[6] The gradient across the outflow tract does not relate to the diastolic thickness of the left ventricular myocardium.

The diastolic contour of the left ventricle in the frontal projection is usually abnormal with a prominent filling defect on the inferior margin and a convexity or an additional filling defect along the left superior margin.[6,50] This abnormality of contour is the result of the asymmetrically hypertrophied septum bulging into the left ventricular chamber (Figure 7). The hypertrophied papillary muscles in some instances are displaced by the asymmetrically hypertrophied septum causing them to have an abnormal orientation relative to the mitral annulus. On the frontal view of the left ventriculogram they are displaced leftward and

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point to the left of the mitral annulus, instead of pointing toward the central axis of the annulus. During diastole, the lateral view characteristically shows an inverted cone in the outflow tract formed

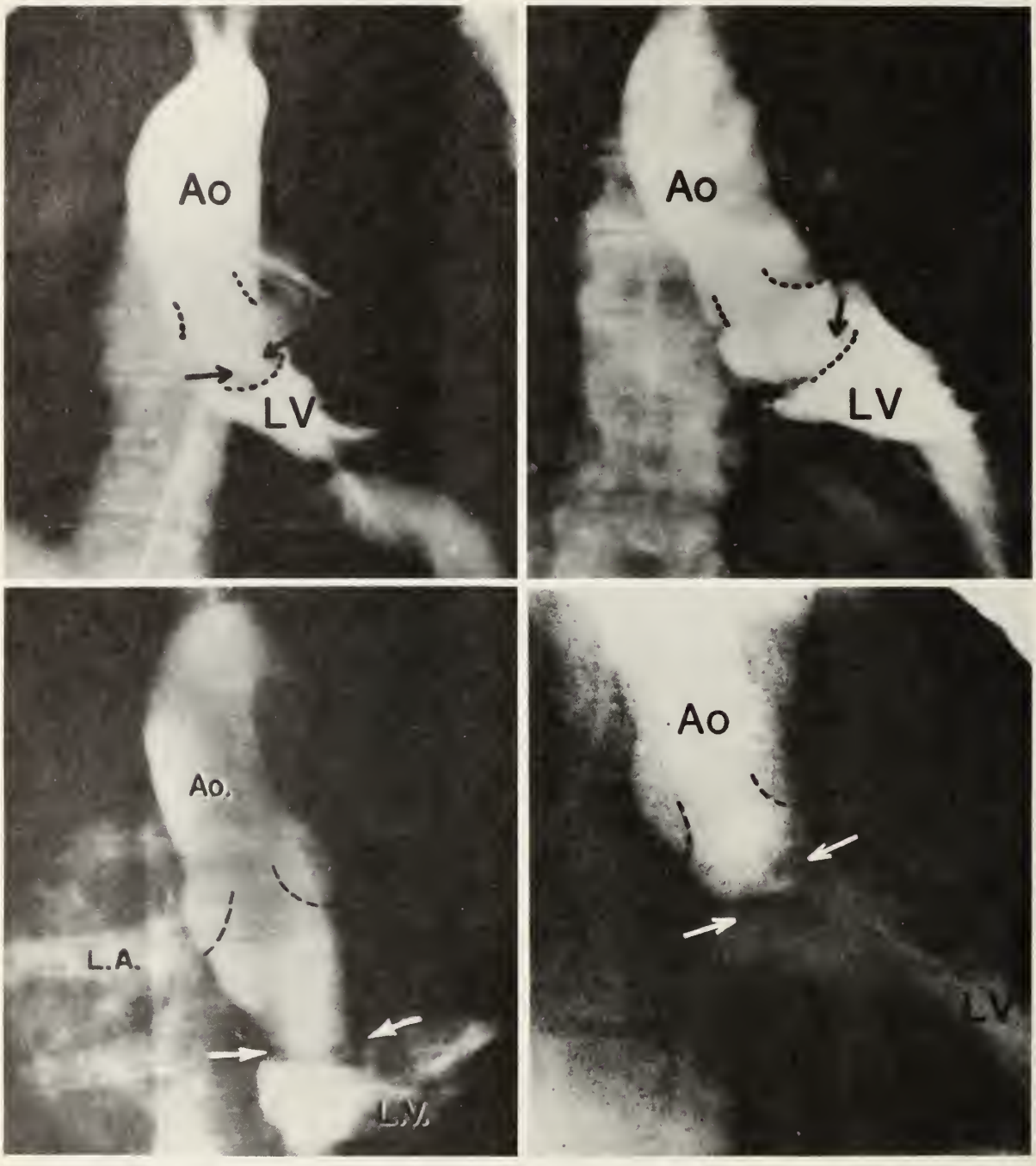

Figure 7.—Frontal frames of left ventriculogram during systole in four patients with the obstructive type of hypertrophic cardiomyopathy. During systole the characteristic contour is caused by multiple structures bulging into the contrast filled chamber. Those on the medial and lateral surfaces near the apex represent the hypertrophied papillary muscles. Those on the medial and lateral sides of the outflow tract **(arrows)** are caused by apposition of the anteriorly tethered and thickened edge of the anterior leaflet of the mitral leaflet and the asymmetrically hypertrophied septum. Prolonged apposition of the latter structures may produce a radiolucent band across the outflow tract **(lower two panels.)** Ao = aorta. LA = left atrium. LV = left ventricle. (Modified and reproduced from Ross J Jr, Braunwald E, Gault JH, et al: Circulation 34:558-578, Oct 1966, with permission of author and American Heart Association, Inc., **In** Grossman W (Ed): Cardiac Catheterization and Angiography. Philadelphia, Lea & Febiger, 1974)

by contrast material between the hypertrophied septum anteriorly and the open anterior leaflet of the mitral valve posteriorly. In part this abnormal contour is due to a closer position of the entire mitral valve apparatus to the ventricular septum in HCM compared to the normal left ventricle.[69]

The end-systolic volume is nearly always less than average and obliteration of all but the proximal part of the inflow tract is frequently observed (Figure 7). The ejection fraction is increased. During systole there is exaggerated circumferential contraction and frequently little apex to base shortening, producing a cylindrical or banana-shaped appearance of the chamber at end-systole. A variety of other bizarre configurations, including septation of the left ventricle into two chambers (hour glass appearance), have been observed during systole.

In obstructive HCM, systolic frames (Figure 7) in the frontal projection display a scalloped, V-shaped or W-shaped radiolucent band across the left ventricular outflow tract.[9,50] This configuration is produced by contact of the thickened leading edge of the anterior mitral valve leaflet against the hypertrophied septum. This mitral valve deformity (anterior tethering in systole) is usually accompanied by a variable degree of mitral regurgitation.[9,70] The lateral view during systole shows the hypertrophied septum bulging into the outflow tract and posteriorly a curved shelf-like deformity (Figure 8) caused by the forward tethering of the anterior leaflet of the mitral valve.[9]

Simultaneous biventricular cineangiograms in the LAO projection facilitate determination of the contour and width of the septum, and in obstructive types of hypertrophic cardiomyopathy they show greater thickening of the septum relative to the posterior left ventricular wall, along with a biconvex contour of the septum.[71] These findings are consonant with the diagnostic echocardiographic findings in this disease—that is, asymmetric septal hypertrophy.

Infusions of inotropic agents exaggerate or induce the obstructive deformity of the outflow tract. Moreover during the infusion of epinephrine and during postpremature beats, the angiographically determined ejection time of the left ventricle is increased rather than decreased as in normal subjects and patients with valvular aortic stenosis, suggesting increased obstruction.

Right ventriculography may show compression and anterior displacement of the right ventricle by the asymmetrically hypertrophied septum.[6,67,72] Either the entire right ventricle or the infundibular portion of the right ventricle may be narrowed by the bulging septum (Figure 9). In advanced cases, the right ventricle has pronounced generalized hypertrophy.

In summary, ventriculography in hypertrophic cardiomyopathies documents the asymmetric septal hypertrophy and hyperdynamic pattern of contraction of the left ventricle. In the obstructive form, the apposition of the thickened anterior leaflet of the mitral valve with the hypertrophied septum produces a characteristic lucent band in the left ventricular outflow tract which is virtually pathognomonic for this disease.

Therapy

DR. ROSS: *Considering the unanswered questions concerning pathophysiology, it is hardly surprising that the principles of therapy for the hypertrophic cardiomyopathies are incompletely understood. We know that hypertrophic obstructive cardiomyopathy is characterized by decreased ventricular diastolic compliance and by variable systolic pressure differences across the outflow tract of the left ventricle. The significance of the systolic pressure gradient is certainly less straightforward than in aortic valve stenosis, and the management of patients with symptoms due to decreased ventricular diastolic compliance is poorly understood. The importance of arrhythmias and the causes of syncope and sudden death remain to be worked out. Dr. Gabriel Gregoratos and Dr. Joseph Utley will summarize the currently accepted principles of medical and surgical therapy.*

GABRIEL GREGORATOS, MD:* Since the discovery by Braunwald and Ebert[73] that drugs with a positive inotropic action on the heart can increase the left ventricular outflow gradient in obstructive HCM, a number of investigators have studied the acute hemodynamic effects of beta-adrenergic blockade in this condition.[74-76] There is general agreement that beta-adrenergic blockade diminishes exercise or isoproterenol-induced augmentation of the left ventricular outflow tract gradient and reduces left ventricular end-diastolic pressure. However, the effects of beta-adrenergic blockade on the resting outflow gradient have been variable and inconstant. Similarly, a beneficial effect on the usual augmentation of the outflow gradient

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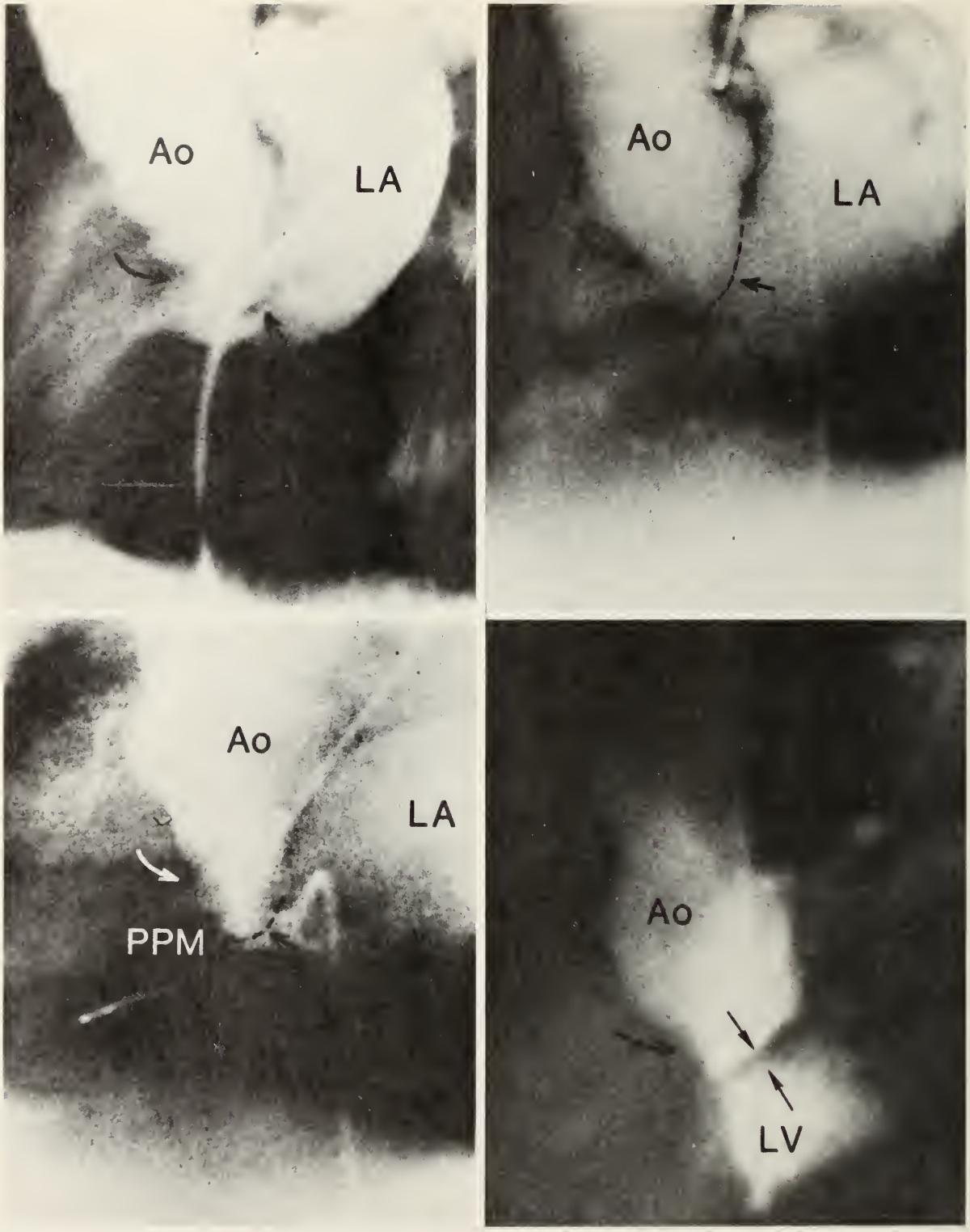

Figure 8.—Systolic frames in the lateral view from four patients with the obstructive type of hypertrophic cardiomyopathy show conical narrowing of the left ventricular outflow tract due to anterior tethering of the anterior leaflet of the mitral valve **(straight arrows)** and bulging of the upper septum **(curved arrows)** into the outflow tract. Ao = aorta. LA = left atrium. LV = left ventricle. PPM = posterior papillary muscle. (Modified and reproduced from Ross J Jr, Braunwald E, Gault JH, et al: Circulation 34:558-578, Oct 1966, with permission of author and American Heart Association, Inc., **In** Grossman W (Ed): Cardiac Catheterization and Angiography. Philadelphia, Lea & Febiger, 1974)

observed after induction of a premature beat has not been consistently found.[77] Findings in more recent studies have emphasized the effects of beta-adrenergic blockade on diastolic events, and there is some evidence that these agents may improve the distensibility characteristics of the left ventricle.[76] Therefore, beta-adrenergic blockade is, theoretically at least, a logical therapeutic approach in HCM since there is little doubt that the major hemodynamic abnormality in many patients is difficulty in filling the left ventricular "chamber" (decreased diastolic compliance), and in some patients difficulty in emptying it as well (systolic outflow tract obstruction).

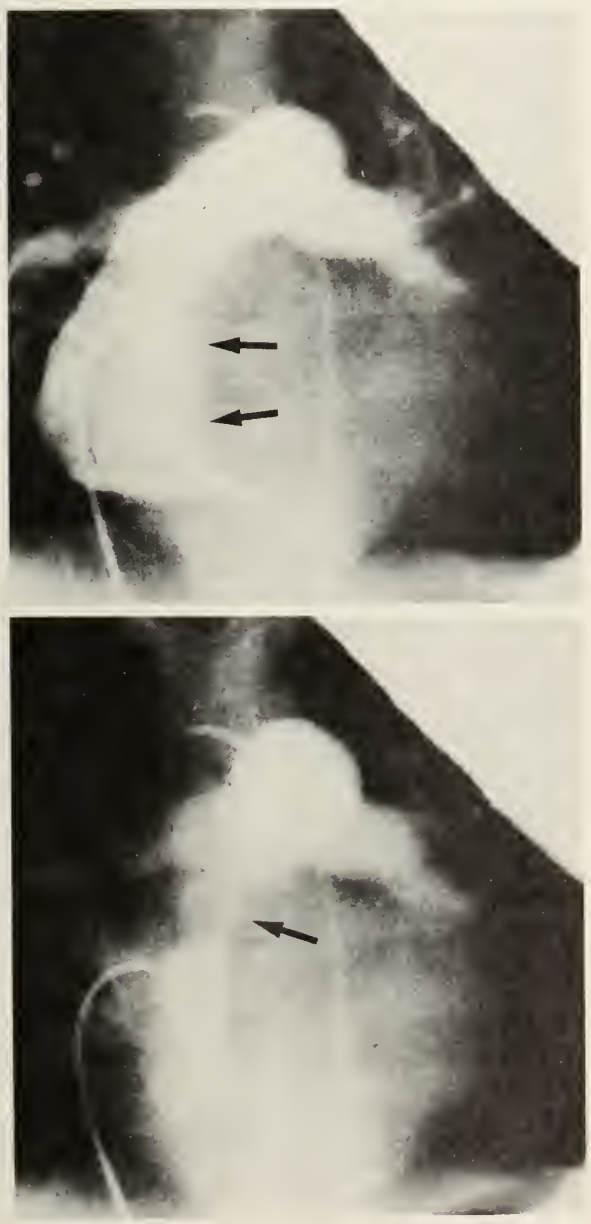

Figure 9.—Right ventriculogram in hypertrophic cardiomyopathy shows narrowing and distortion of the right ventricular outflow tract by the bulging septum **(arrows)**. Diastole **(above)**, systole **(below)**. Note the narrowing of the right ventricular outflow tract during systole **(arrow)**.

Propranolol

During the 1960's, favorable clinical results of long-term propranolol therapy in patients with obstructive HCM were reported. In more recent studies, it was found that while in most patients there was some initial improvement, with amelioration of angina and improvement in effort tolerance, this improvement was not always maintained.[78] Only 42 percent of patients reported in the recent literature have had sustained clinical improvement while taking propranolol. In a study of 13 patients with HCM treated with propranolol and followed an average of 17 months, Stenson and co-workers found initial symptomatic improvement in most: angina pectoris decreased in six of eight patients, dyspnea improved in eight of ten patients and palpitation diminished four of six patients.[79] However, three patients with an initially good response had a return of symptoms during the period of study. The authors concluded from serial clinical observations and hemodynamic studies in nine of the 13 patients that propranolol exerted a favorable effect on symptoms but did not change the course of the underlying disease. A report by Wigle and co-workers concerned 32 patients with obstructive HCM, 22 with evidence of left ventricular outflow obstruction at rest and 10 with latent (provocable) outflow gradients,[78] who were treated with propranolol and followed for an average of 30 months. In most patients there was initial improvement, but in only eight of 22 patients with left ventricular pressure gradients at rest was the improvement sustained. In contrast, in all ten patients with latent obstruction symptomatic improvement occurred and in seven there was complete and sustained relief of symptoms.

The usual dose of propranolol has ranged from 120 to 320 mg per day in divided doses; the effective dose averages 40 mg four times a day, although the dosage should be individually determined for each patient. Adequacy of beta-adrenergic blockade and patient compliance in taking the medication have been gauged in most studies by the development of resting bradycardia of between 50 and 60 per minute.

Assessment of the effects of beta-adrenergic blockade on the clinical signs of hypertrophic

obstructive cardiomyopathy is difficult. The variability of the systolic ejection murmur from day to day, as well as its tendency to diminish or disappear with progression of the disease, make it a particularly unreliable sign to follow during propranolol treatment. Therefore, attention has been focused upon noninvasive techniques such as echocardiography. Shah and co-workers reported that 19 patients receiving long-term oral propranolol therapy had no significant change in the abnormal systolic anterior motion of the mitral valve.[80] In a trial of propranolol and practolol it was shown that mitral valve motion, especially the diastolic closure (EF) slope, tended to return toward normal during therapy.[81]

The treatment of asymptomatic patients with HCM remains controversial. Goodwin and Oakley suggest treatment of asymptomatic patients with propranolol in an effort to reduce the stimulus to further hypertrophy and decrease the likelihood of sudden death.[82] Despite the theoretical attractiveness of this position, the potential for adverse drug reactions resulting from long-term use of propranolol is always present. Preliminary results of long-term follow-up studies in children with asymptomatic hypertrophic obstructive cardiomyopathy suggest that the risk of sudden death is not inconsequential,[16] but unfortunately neither propranolol nor surgical myectomy completely protected against sudden death. Therefore, the roles of prophylactic propranolol or surgical treatment in asymptomatic patients with hypertrophic obstructive cardiomyopathy remain to be established. In general, HCM is a progressive disease,[79,83] despite its wide range of clinical expression. Excluding surgical mortality and unrelated deaths, the annual attrition rate was reported as 3.4 percent in the cooperative multicenter study.[17] It is important, therefore, to consider whether or not available pharmacologic agents can delay or arrest this progression. However, none of the clinical studies reported so far document such an effect.[16-17,79,81] Consequently, the use of prophylactic propranolol in asymptomatic individuals with HCM remains controversial. Perhaps newer pharmacologic agents (see below) may offer a better form of prophylactic treatment.

Patients with nonobstructive HCM often have complaint of angina pectoris, effort dyspnea, syncope or presyncope, and infrequently frank congestive heart failure develops. There is evidence that propranolol, by reducing myocardial oxygen requirements, will favorably alter the balance between myocardial oxygen supply and demand and thereby relieve angina pectoris in this group of patients, as it does in patients with coronary artery disease.[16,78] So far, controlled studies of the effects of such treatment in this subgroup of patients are lacking. Propranolol also has been reported to be effective in alleviating syncope and presyncope in patients without obstruction, but it is less effective in affording symptomatic relief in patients who are limited mainly by exertional dyspnea or fatigue.[16]

Treatment of Atrial Fibrillation

The onset of atrial fibrillation usually heralds progression of the disease to a serious stage.[30,83] Atrial fibrillation is deleterious for two reasons: first, the relatively nondistensible hypertrophied left ventricle is dependent on normal atrial contraction for optimal diastolic filling; and second, the resulting rapid heart rate further restricts filling by reducing the ventricular diastolic filling period; impaired relaxation of the hypertrophied ventricle at rapid rates may even further impair diastolic filling. Rapid atrial fibrillation may result, therefore, in a sudden catastrophic increase in left atrial pressure, with pulmonary edema or sudden death.[83] The risk of systemic embolization under these circumstances also is considerable.[84] Prompt restoration of regular sinus rhythm, therefore, is the prime objective when atrial fibrillation has occurred, and direct current cardioversion should be carried out as soon as possible. Cardioversion is usually successful, but maintainance of regular sinus rhythm may be difficult.[83] The use of propranolol or other antiarrhythmic agents may be of help in maintaining sinus rhythm.

In general, the use of digitalis glycosides in patients with obstructive HCM is not advocated because of their positive inotropic action, which carries the potential of further increasing left ventricular outflow obstruction. However, in the face of rapid atrial fibrillation, if immediate cardioversion is not available, slowing of the ventricular rate to below 120 per minute is of paramount importance and small doses of digitalis and propranolol constitute an acceptable alternative treatment.

Management of Congestive Heart Failure Phase

It has been suggested by Goodwin that in approximately 10 percent of patients with HCM there is progression to a phase where outflow tract obstruction is no longer present. This is accom-

panied by disappearance of the outflow tract murmur and development of symptoms of congestive heart failure, with or without atrial fibrillation.[83] However, in the multicenter cooperative study on the "natural (and unnatural) history of hypertrophic obstructive cardiomyopathy," the development of clinical features dominated by congestive heart failure with loss of outflow obstruction was extremely rare.[17]

Diuretics are helpful in the presence of severe congestive symptoms, although care must be taken to avoid excessive diuresis which can result in severe reduction of left ventricular filling pressure. The use of digitalis remains controversial and is best avoided unless there is clear hemodynamic evidence of the absence of a latent left ventricular outflow tract gradient.

Prophylaxis Against Infective Endocarditis and Thromboembolism

Infective endocarditis is a well-recognized complication of HCM.[17,85,86] It usually occurs on the mitral valve and several fatalities have been reported. Therefore, it is recommended that patients with HCM should receive the same prophylactic antibiotic regimen with dental and surgical procedures as those patients with other forms of valvular or congenital heart disease. The recommendations of the American Heart Association Committee on Endocarditis and Rheumatic Fever Prophylaxis should be followed.[87]

Anticoagulation

Systemic embolization has been reported in patients with HCM and atrial fibrillation,[84] and it appears that the incidence of embolism with atrial fibrillation is higher than with atrial fibrillation in other forms of heart disease.[81] Consequently, anticoagulant therapy should be started immediately and continued indefinitely once atrial fibrillation has developed in a patient with HCM.[83] It is recommended by Goodwin that anticoagulant therapy also be initiated in patients whose history suggests paroxysmal atrial fibrillation but who are found to be in sinus rhythm at the time of cardiac evaluation.[83] However, documentation of paroxysmal atrial fibrillation by means of ambulatory ECG monitoring would seem desirable before committing a patient to chronic anticoagulation.

Prevention of Sudden Death

Sudden, unexpected death is a most important feature of the natural history of HCM. In the multicenter cooperative study on the natural history of this disease, sudden death was the most common single cause of mortality (26 of 49 deaths). In all, 18 percent of patients taking propranolol and 16 percent of patients receiving no treatment died suddenly,[17] and it was concluded that propranolol afforded no protection against this complication. The mortality of the medically treated and untreated groups (average 17 percent) was contrasted with a 5.2 percent incidence of sudden death in the surgical group—a significant difference ($p<0.05$) suggesting some protection by ventriculomyotomy. There are no good predictive signs for this catastrophe,[81] and sudden death has been reported in asymptomatic or minimally symptomatic patients independent of the functional class and the degree of left ventricular outflow obstruction.

The mechanism of sudden death in HCM is unclear. Recently, Goodwin and Krickler[88] proposed that primary arrhythmias may be responsible for at least a portion of the sudden cardiac deaths encountered in this condition. The recognition that "latent" preexcitation may be present lends support to the assumption that reentrant arrhythmias may play an important role.[88] Certainly, symptoms of palpitation are well-recognized in patients with HCM. Adequate data on long-term electrocardiographic monitoring of patients with this disorder are not available. However, in a patient complaining of symptoms of abnormal heart action, documentation of possible arrhythmias by means of ambulatory monitoring is indicated, with appropriate antiarrhythmic therapy being instituted once the arrhythmia has been defined. In the presence of preexcitation, complete assessment by electrophysiologic studies of conduction abnormalities and effects of combinations of drugs may be necessary.

High-grade atrioventricular (A-V) block has rarely been documented in association with HCM or shown to be a cause of syncope,[89,90] but it is likely that at least some of the reported cases of sudden death may have been due to a high-grade A-V conduction disturbance. When high-grade A-V block is documented, the treatment of choice is electrical pacing. The value of sequential atrioventricular pacing in maintaining adequate cardiac output by preserving left atrial contraction has been recently emphasized.[89]

Newer Therapeutic Approaches

The effects of verapamil, a specific membrane-active calcium antagonist, are being investigated. In a recently-reported clinical study,[90] 20 patients

with hemodynamically and angiographically documented obstructive HCM were treated first with beta-adrenergic blockade for 20 months and then with verapamil (480 mg per day) for an average of 12 months. Greater improvement in symptoms with verapamil was reported. Objectively, significant reduction in electrocardiographic evidence of left ventricular hypertrophy and radiologically measured heart volume were also documented following verapamil therapy. The investigators concluded that treatment of hypertrophic cardiomyopathy with verapamil was superior to use of propranolol. Obviously, additional experience with this promising agent is necessary.

Another recently investigated form of therapy consists of electrical stimulation of the apex of the right ventricle. In four patients with proven hypertrophic obstructive cardiomyopathy, Hassenstein and co-workers[91] reported a 56 percent reduction of the left ventricular outflow gradient during ventricular pacing. Optimal results were achieved through the use of an atrial-synchronous pacemaker, with short atrioventricular conduction times. Further investigation and confirmation of these findings will be necessary before these methods can be widely applied in clinical therapy.

Surgical Treatment

JOSEPH UTLEY, MD:* Surgical treatment of HCM with obstruction has been directed principally at relieving the obstruction to the left ventricular outflow by resecting the hypertrophic septal muscle.[92] As the role of the anterior leaflet of the mitral valve has been better understood in the mechanism of obstruction, mitral valve replacement also has been proposed as a surgical treatment for this disorder.[93]

Surgical treatment is generally recommended for patients with asymmetric septal hypertrophy and a pressure gradient, whose symptoms are poorly controlled by beta-adrenergic blocking agents. Generally, 10 percent to 15 percent of patients with the obstructive form of HCM are candidates for surgical therapy. HCM may occur in conjunction with other cardiac lesions, including coronary artery disease, aortic valve stenosis, mitral stenosis and insufficiency and congenital heart defects. The correction of associated defects is most important, because failure to correct them, particularly coronary artery stenosis, may lead to poor symptomatic relief.

A variety of approaches has been used for septal muscle excision. The muscle has been resected through the right ventricle, the apex of the left ventricle, the detached anterior leaflet of the mitral valve, and the root of the aorta and aortic valve. Approaches through the right ventricle and mitral valve have failed to relieve the obstruction. The apical left ventriculotomy approach produces excellent relief of obstruction but often impairs left ventricular function. The best approach is septal muscle resection through the aortic root and aortic valve (Morrow procedure).[92] Morrow and his associates have shown that septal muscle resection produces excellent symptomatic results, eliminates systolic pressure gradients and diminishes mitral insufficiency.[92,94] The most frequent complication of transaortic septal myectomy is left bundle branch block. Less common are complete heart block or a small ventricular septal defect. The mechanism by which obstruction and mitral regurgitation are relieved is not fully understood, but removal of hypertrophied septal muscle and the consequent realignment of the anteriorly displaced papillary muscles are thought to play an important part.

Cooley has recommended mitral valve replacement as the definitive treatment for obstructive HCM.[93] This approach has not been generally accepted because of the excellent results of transaortic septal myectomy, the long-term complications of low profile mitral valve prostheses and the need for anticoagulation. Mitral valve replacement may be the procedure of choice in patients with HCM and severe mitral insufficiency due to the disease itself, and it is indicated when the regurgitation is secondary to rheumatic valvulitis, ruptured chordae or bacterial endocarditis. Patients with mitral insufficiency, coronary artery disease and diminished left ventricular function may be better managed by mitral valve replacement because of the risk of septal muscle damage and infarction in some patients undergoing transaortic septal myectomy.

Preoperative conduction disturbances including right bundle branch block, intermittent or permanent A-V block and incomplete left bundle branch block should not be indications for mitral valve replacement. If complete heart block results from the transaortic septal myectomy, the patient can be managed well using a permanent pacemaker, which is preferable to insertion of a mitral valve prosthesis.

Cooley has emphasized the importance of using

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a low profile prosthesis, such as the Bjork-Shirley or the Cooley Cutter valve, for mitral valve replacement in patients with HCM. Certainly, a ball valve prosthesis is contraindicated because of the volume it occupies in the diminished left ventricular cavity. The hemodynamic effects of a Hancock porcine heterograft in patients with HCM with obstruction are not well known, but the lack of requirement for anticoagulation make them advantageous in some patients. Anesthesia should include halothane and use of alpha adrenergic pressor agents such as phenylephrine hydrochloride (Neo-Synephrine). β-adrenergic drugs should be avoided intraoperatively.

Developments in techniques of cardiopulmonary bypass, hemodilution and myocardial protection have improved the results of both septal muscle excision and mitral valve replacement in recent years. Cardiopulmonary bypass is conducted at 28°C, at low flows (1.6 liters per minute per sq meter) and at a hematocrit of 20 percent to 25 percent. In most adult patients, it is possible to remove 500 to 1,000 ml of whole blood before beginning cardiopulmonary bypass and by using low priming volume oxygenators the hematocrit during bypass will be between 20 percent and 25 percent. After the termination of bypass, the oxygenator volume is slowly infused into the patient, adding furosemide to increase urine output if necessary and monitoring left ventricular filling pressure with a Swan-Ganz catheter or left atrial catheter. The blood removed before bypass is then slowly infused. This technique of hemospasia makes many cardiosurgical procedures possible without homologous blood transfusion. The blood drawn before cardiopulmonary bypass is rich in platelets and other coagulation components, because it has not been exposed to the pump-oxygenator. Postoperative bleeding is greatly diminished with this technique.

The recently popularized technique of cardioplegic aortic root perfusion for myocardial protection is particularly suitable for operations in patients with ventricular hypertrophy. This technique involves the infusion of cold solutions through the coronary circulation via the root of the aorta. The cold (5°C) solutions are typically high in potassium (20 to 40 mEq per liter) and contain substrates (glucose and insulin) in a physiologic solvent (Ringer's lactate). The adequacy of myocardial perfusion is determined by the absence of electrical and mechanical action and the cold, flaccid myocardium. The flaccid heart muscle produced by cardioplegia is particularly helpful when operating on the thickened, hypertrophied muscle that characterizes HCM. Transaortic septal myectomy and mitral valve replacement also are much easier and safer when the myocardium is flaccid.

After infusion of the cardioplegic solution, the aorta is opened obliquely into the noncoronary sinus. The aortic valve is retracted with small ribbon spatula retractors. A wedge of septal muscle, 1.0 to 1.5 cm wide and 4.0 cm long, is excised below the junction of the left and right coronary cusps anterior to the papillary muscle to within 1 to 2 cm of the left ventricular apex. An index of the adequacy of the excision is the visualization of the left ventricular apex from the aortic valve. The muscular incision is carefully controlled using a #13 Bard Parker blade. Septal myotomy alone does not relieve the pressure gradient and muscle excision (myectomy) is always necessary.

The results of septal myectomy have been excellent in terms of symptomatic relief and physiologic correction of the obstruction.[92,95,96] Overall operative mortality has been 7 percent[92] but more recently is 3 percent or less, and late cardiac deaths are unusual. Virtually all patients have been symptomatically improved; systolic pressure gradients at rest are zero in about 90 percent of patients in whom studies are done postoperatively and rarely greater than 25 mm of mercury, while provocable gradients are usually less than 50 mm of mercury.[92] Left atrial size diminishes in most patients and is associated with reversion to sinus rhythm in some patients. Late studies (up to 14 years) have not shown recurrence of obstruction.[92]

In summary, septal myectomy is a safe surgical procedure for the treatment for HCM with obstruction in symptomatic patients refractory to medical therapy. Mitral valve replacement is the procedure of choice in only a few patients with poor ventricular function, coronary artery disease and predominant mitral insufficiency, particularly if the regurgitation is due to endocarditis or ruptured chordae tendineae.

Summary

DR. ROSS: *In summary, we can say that hypertrophic cardiomyopathy* (HCM) *is a disease whose features are now reasonably well recognized. Pathologically, there is asymmetrical hypertrophy of the interventricular septum, accompanied by histologic evidence of disorganization of muscle cell arrangement in the septal region, and some-*

times there are secondary changes in the mitral valve. We learned early that it was necessary to measure pressure gradients within the left ventricle at rest, or during provocation, by positioning the catheter in the left ventricular inflow *tract and not at the apex of the ventricle, which can lead to artifactual gradients; we also found that there was a typical angiographic anatomy of the left ventricle, and in obstructive* HCM *apposition of the anterior leaflet of the mitral valve against the intraventricular septum during systole was found to cause the obstruction as well as mitral regurgitation.*[9,50] *Subsequently, echocardiographic diagnosis of* HCM *became feasible with the recognition of asymmetric septal hypertrophy* (ASH), *and this finding was extended to allow recognition of a high incidence of the genetic form of the disease.*[16] *The common association of systolic anterior motion* (SAM) *of the mitral leaflet with hemodynamic evidence of obstruction also became clear. We now recognize, however, that neither* ASH *nor* SAM *of the mitral valve are pathognomonic, both sometimes occurring in other diseases as well as in concentric left ventricular hypertrophy. The clinical features of* HCM, *including left ventricular hypertrophy (often with unusual electrocardiographic features which can suggest previous myocardial infarction) and, when present, the signs of dynamic outflow tract obstruction, including the characteristic bifid carotid pulse, an ejection systolic murmur at the lower left sternal border which increases with the Valsalva maneuver, during standing, or a postextrasystolic beat, all aid in the diagnosis. It is now generally possible, therefore, to recognize without cardiac catheterization whether or not a patient has the disorder, whether it is the nonobstructive or obstructive type, and whether or not it is the genetic form. Once recognized, it is then feasible to identify and treat those patients whose symptoms may be alleviated with propranolol, or by antiarrhythmic therapy, and to select those few patients with the obstructive form who will benefit from surgical treatment.*

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The Bottom Line Syndrome
Hypertrophic Cardiomyopathy Revisited

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THE PROLIFERATION of biomedical literature leads many of us into bad habits. Faced with the impossibility of keeping up, we tend to read the abstract rather than the full article, seeking the "bottom line." On the other hand, review articles, such as that by Shabetai and co-workers in this issue of the journal, require that interested readers digest a meatier text. Many of us breathe a sigh of relief when we encounter such a comprehensive article, summarizing upwards of 100 well-chosen references (which we now do not have to read).

However, we must be wary of the bottom line syndrome even when we read comprehensive review articles, because the authors cannot avoid bias in presenting what they sincerely believe to be the bottom line in a clear and understandable manner. The bottom line that will be carried away by the reader of Shabetai's article is that there is a "dynamic obstruction to outflow" of the left ventricle, and that it therefore must be a significant manifestation of hypertrophic cardiomyopathy (HCM).

Having an admitted bias against this "obstructionistic" viewpoint, and realizing that few readers will bother reading the 96 references cited, I will take the editorialist's prerogative to present the other side, going over some of the same ground with differing emphasis. My bottom line is "an obstruction, if present, has little or nothing to do with the morbidity and mortality from HCM."

Discovery

Brock's[1,2] discovery in the late 1950's of the condition now known as hypertrophic cardiomyopathy sparked two decades of investigation, prolific documentation and unresolved controversy. The premortem recognition of HCM required techniques which only came into existence in the past 25 years, hence its relatively late discovery, considering the apparent prevalence of the condition. Brock's pioneering discovery resulted from observations made at left heart catheterization and during intracardiac surgical procedures, techniques then in their infancy. As left heart catheterization and selective angiocardiography became widespread, a flood of observations and interpretations came forth. A more recent resurgence of interest followed the advent of conventional echocardiography, and it can be predicted that two-dimensional echocardiography will spark yet another era of discovery and controversy.

The Controversy

It may be surprising to some that any significant controversy should remain after all of this modern technology has been brought to bear on this disease entity. The heart of the controversy is the role of obstruction in the pathophysiology of the disease. The focus of virtually every article written in the formative years of our knowledge of HCM as well as the current review article is on the primacy of obstruction. The sheer weight of these articles, in which HCM was referred to as functional obstruction of the left ventricle,[1,2] pseudoaortic stenosis,[3] functional aortic stenosis,[4] muscular subaortic stenosis,[5] idiopathic hypertrophic subaortic stenosis (IHSS),[6] obstructive cardiomyopathy,[7] diffuse subvalvular aortic stenosis[8] and subaortic hypertrophic stenosis[9] renders the task of challenging the pivotal role of obstruction difficult. It is hoped that a careful reading of this editorial (and the supporting references) will show that the case for obstruction remains cir-

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cumstantial, and that continued challenge and open-minded investigation is justified.

A Reexamination of the Original Case for Obstruction

A reexamination should begin with Brock's[1,2] and Teare's[10] articles, which introduced HCM to the medical literature. Brock, contrary to popular belief, *failed to find any obstruction* while thoroughly exploring the outflow tract of the beating heart with bougies and fully expanded dilators passed through the left ventricular apex:

> A 4 mm bougie was passed and encountered no obstruction and could be moved freely from side to side. The same findings were obtained with a 7 mm bougie. Finally an expanding dilator was passed and was opened gently in the valvar and subvalvar regions and encountered no sense of resistance; it could be moved up and down freely.[2]

Although he bracketed these manipulations with pressure withdrawal tracings to confirm the persistence of the gradient, he was repeatedly unable to find any obstruction in the four patients he operated upon, three of whom died. He stated "the functional nature of the obstruction is concealed in death. Indeed it is concealed in life unless we are able to document its presence by means of a pressure withdrawal record."[2]

Brock began his second article describing the skepticism with which his first article was received citing that there was ". . . doubt about the very occurrence of functional obstruction of the ventricle." He referred the reader to his earlier classical studies on right ventricular infundibular stenosis complicating pulmonic stenosis. He was cognizant of the important anatomical differences between the muscular right ventricular infundibulum and the noncontractile subaortic vestibule, but stated that "below this rigid vestibule the walls of the outflow tract are chiefly muscular and, when sufficiently hypertrophied, they can come together at an early stage of systole and constitute an obstruction to the continued emptying of the left ventricle." He offered as sole proof of this obstruction the pressure gradient on catheter withdrawal recordings, despite the fact that his meticulous exploration of the beating heart failed to find the elusive sphincter. Thus Brock's "bottom line" that the gradient proved the existence of an obstruction established a bias that could not fail to influence future investigators studying HCM.

Teare's[10] original article entitled "Asymmetrical hypertrophy of the heart in young adults" (submitted for publication before Brock's first article) pointed out the inordinate septal hypertrophy with bizarre cellular disarray in nine patients, eight of whom had died suddenly, but he made no mention of outflow tract narrowing or obstruction. Later, while describing his pioneering studies on the "tumour-like" septum he said "A bizarre and disorderly arrangement of bundles of muscle fibres runs in divers directions . . . giving the impression of inefficiency in muscular contraction of the tumour as a whole. . . ." In the ensuing discussion of his paper Dr. John Goodwin questioned this "inefficient contraction." citing the tremendous pressure generation and high output of the left ventricle to the contrary. Dr. Teare replied ". . . one gets the impression, looking at these sections, that bundles of muscles are all pulling in different directions rather than together, but if you say that in fact they produce a powerful ejection, I naturally accept it."[11]

In the next five years, Brock's observation that a pressure gradient could develop in the left ventricle was repeatedly confirmed in laboratories all over the world, and the unique characteristics of the phenomenon were explored. The gradient increased with inotropic stimulation or by decreasing preload or afterload, and the gradient could be decreased by increasing the preload or afterload. "Gradient" and "obstruction" were considered synonymous by all but a few authors.

Selective angiocardiograms purporting to show the muscular sphincter as a conical or hourglass narrowing of the outflow tract were published,[12-15] and the tip of the cone was considered to be the site of obstruction.[14,15] Surgical descriptions of the muscular sphincter followed: "Forceful contraction of the outflow tract on the beating finger is evident during systole" (Morrow).[15] "Upon making a small apical ventriculotomy, palpation with the finger of the ventricular chamber showed a small apical chamber. During systole, the musculature of the outflow tract contracted over a long segment, squeezing the operator's finger to a degree which could only be duplicated with some effort within the fist of the other hand" (Julian).[16] "That this obstruction is dynamic is immediately appreciated by the surgeon who passes his finger down through the obstruction in a beating heart. The compression around the finger is nothing short of painful" (Dobell).[17]

By the mid-1960's, the case for a muscular sphincter which progressively narrowed during systole and obstructed left ventricular outflow

seemed firmly established,[15] and the equation *pressure gradient = obstruction* seemed secure, in light of angiographic "cone" and the surgical proof of the muscular sphincter.

The Challenge

The equation was questioned[18] by Hernandez and co-workers in 1964. They stated

> the intraventricular pressure drop characteristic of these patients has led to the postulate that obstruction takes place in systole because of a constricting ring of hypertrophied muscle in the outflow tract of the left ventricle below the aortic valve. This pressure drop, however, is not in itself proof of a discrete obstruction in the infundibulum. An abnormally powerful and rapid contraction of the ventricle may possibly produce almost total ejection early in systole so that late in systole there remains a virtually empty ventricle contracting on the catheter tip trapped in small, isolated pockets of blood among the trabeculae . . . careful ventricular volume studies will be necessary to settle this question.[18]

Gauer,[19,20] working in animals with hypovolemia, had previously shown that regions of high intraventricular pressure can be generated when "the ventricle continues to contract after having expelled its pathologically small blood content." Cineangiographic studies in patients with HCM and pressure gradients showed the following: (1) The ventricle emptied more rapidly and completely than the normal. (2) When the gradient was increased after premature beats or isoproterenol infusion, more rapid and more complete emptying resulted. (3) The "conical" or "hourglass" narrowing of the left ventricle displayed by other authors was in fact a *diastolic* event. (4) There was no angiographically demonstrable systolic muscular narrowing of the outflow tract.[21,22]

The intraventricular pressure gradient was attributed to "cavity obliteration," the phenomenon described by Gauer in which the ventricle expels its blood rapidly and then continues to exert pressure isometrically in late systole in contractile regions of the ventricle (the body and the apex) while the noncontractile region (the aortic vestibule) maintains a lower systolic pressure equal to that in the aorta. The angiographic findings (high ejection fraction rapidly expelled) supported this concept since they frequently showed virtual obliteration of the cavity of the left ventricle[15,21,22] to within a few centimeters of the aortic valve which offered an explanation for the squeeze on the surgeon's finger[15-17] as well.

Although the term "cavity obliteration" has been used consistently by this author to describe the pressure phenomenon in which the virtually obliterated portions of the left ventricle created a higher intracavitary pressure than that in the noncontractile subaortic region,[21-23] other authors later substituted the term "catheter entrapment."[26,27] This change in terminology implied that the observed pressure phenomenon was artifactual and in some way caused by compression or distortion of the catheter. It was and still is our contention that these pressures are *not* artifacts, but represent true pressure conditions in the ventricle.[23]

The Rebuttal—Emergence of the Mitral Valve as the New Site of Obstruction

These articles which challenged the holy triad of IHSS-HCM (the pressure gradient, the angiographic cone and the surgeon's sphincter) sparked considerable rebuttal, during which the sphincter or contraction ring[15-17] was replaced by mitral valve-septal apposition as the site of obstruction.[24] This subtle shift is not apparent to the "bottom line" reader, since the muscular sphincter was not formally renounced—the new obstruction quietly took its place.

Echocardiography showed that the thickened septum, which was the prime mover in the old contraction ring was in fact almost inert, and that the active part of the new obstruction was apparently the systolic anterior movement (SAM) of the mitral valve.[25] The same angiographic frames used to show the "old"[28(Fig. 6)] obstruction were merely republished with newly positioned arrows pointing to the "new" obstruction.[24]

The "bottom line" emerging from the rebuttal was that there is indeed an obstruction, and its presence can be "proved" hemodynamically by placing a transseptal catheter in the inflow tract,[24] or just inside the mitral valve,[26] a catheter position which is purported to rule out "catheter entrapment."[26,27] Angiocardiographic demonstrations of a "lucent line" representing anterior leaflet-septal apposition and echocardiographic systolic anterior motion (SAM)[24] seemingly provided the anatomical clinchers.

It is of interest to note that the surgical approach to the "new" site of obstruction remained essentially the same as it had been when the obstruction was a contraction ring: incision and resection of a strip of muscle from the hypertrophied septum. In 1964 Morrow stated "when obstruction to outflow existed, it resulted from the contraction of the abnormal muscle mass during systole," and described and illustrated (in Figures

117 and 118) the "contraction ring."[15] In 1975 he stated "the operative method presently utilized to relieve outflow tract obstruction in IHSS is similar in principle to the technique of left ventriculomyotomy and myectomy described in 1964."[29]

Current Status of the Nonobstructive Concept

Before accepting the "bottom line" espoused anew in the current review article, the reader is advised to ponder some of the following dilemmas, many of which are mentioned (but might be overlooked by a "bottom line" reader) in Shabetai's article: (1) HCM patients without pressure gradients (and therefore without obstruction) often have as much or more hypertrophy, may be as or more symptomatic and may have a significantly higher mortality than those who do.[30] (2) The left ventricle in HCM empties more rapidly and more completely than the normal[22-24,31] (see Figure 4 of the review article), a finding that challenges the accepted definition of obstruction. (3) Echocardiographic "SAM" is seen in non-HCM ventricles without "obstruction," and may not always represent anterior mitral leaflet, but chordae or papillary muscles,[32] which may oppose the septum without obstructing outflow. (4) Pressure gradients indistinguishable from those seen in HCM can be recorded in normal ventricles without any evidence of obstruction,[19,20,23,33] when the ventricle contracts excessively due to inotropic stimulation combined with reduced preload or afterload. (5) An angiographic "lucent line" representing "SAM" can be produced in experimental animals by creating a chronically hypertrophied ventricle which empties vigorously,[34] and therefore may result from distortion of the mitral valve in an excessively contracted left ventricular cavity.

The evidence that a significant obstruction exists (that is, one that *impedes* left ventricular emptying), and that it is responsible for the morbidity and mortality in HCM is still not established 21 years after its discovery. And that is the bottom line.

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Refer to: Epstein WV, Rizk N: Amyloidosis—Medical Staff Conference, University of California, San Francisco. West J Med 130:354-359, Apr 1979

Amyloidosis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *The topic for this staff conference is amyloidosis, and the case summary will be given by Dr. Norman Rizk.*

DR. RIZK:† The case is that of a 35-year-old black woman, a postal clerk, who presented to the Moffitt Hospital with the chief complaints of malaise, fatigue and a 45-pound weight loss.

The patient was in good health until the fall of 1976, when symptoms of malaise, fatigue and abdominal bloating developed. She had an apparent viral illness in the fall of 1977 and subsequently lost 45 pounds over eight months. In January 1978 dull substernal chest pain began to occur; the patient sought attention at another hospital where cardiac examination showed a loud S_3 and a systolic ejection murmur. Findings on an electrocardiogram were consistent with an anteroseptal myocardial infarction. An x-ray study of the chest showed cardiomegaly. A cardiac catheterization carried out at that time showed a concentrically hypertrophied left ventricle with a cardiac output of 4.5 liters, a cardiac index of 3.2 liters per sq meter and an ejection fraction of 75 percent. The pulmonary capillary wedge was 22 mm of mercury and the left ventricular end diastolic pressure was 15 mm of mercury. There were no valvular lesions identified, and the attending cardiologist felt that a concentrically hypertrophied left ventricle of unknown cause was present. The patient continued to lose weight.

She was referred to the University of California, San Francisco (UCSF), Renal Clinic because of a serum creatinine value of 3.2 mg per dl. The hematocrit then was 36 percent, and the sedimentation rate was 82 mm per hour. Findings on serological studies, including antinuclear antibodies, rheumatoid factor, serum complement and thyroid function studies, were within normal limits. Analysis of a urine specimen in the clinic then showed 3+ protein. By August 1978 the creatinine value had risen to 4.3 mg per dl. The patient was admitted at that time to UCSF Medical Center for investigation of the rising creatinine level, cardiomegaly and complaints of weight loss, fatigue and abdominal bloating. Past medical history, family history and social history were unremarkable. The review of systems was noncontributory.

On physical examination the patient was thin, pleasant and in no acute distress. Blood pressure was 130/100 mm of mercury, pulse was 120, temperature was 37°C (98.6°F) and respirations were 14. On head, eye, ear, nose and throat examination it was noted that pupils and fundi were normal, and that there was a diffusely enlarged, nontender thyroid gland. There was no lymphadenopathy. The skin showed no purpura. The chest was clear to percussion and auscultation. Cardiovascular examination showed no jugular venous distention, the point of maximal impulse

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†Norman Rizk, MD, second-year medical resident.

was laterally displaced at the sixth intercostal space in the anterior axillary line. There was a normal S_1 and S_2, and a loud S_3; a 2/6 systolic ejection murmur was present at the left sternal border. The abdomen was found to be soft and nontender, without hepatosplenomegaly. Pelvic examination showed normal external and internal genitalia. Findings on neurological examination were normal, including no evidence of peripheral neuropathy.

Initial laboratory data included a hematocrit of 30.4 percent, a leukocyte count of 6,900, with a normal differential. Platelets were 417,000. The blood urea nitrogen value was 77 mg per dl and the creatinine value was 5.2 mg per dl. The albumin level was 3.3 grams per dl. Analysis of urine showed 2+ proteinuria without cells or casts. Cardiomegaly was shown on an x-ray study of the chest, and an electrocardiogram showed a sinus tachycardia with a rate of 110. There was a first degree atrioventricular block with a PR interval of .24. QS complexes were present in V_1 through V_4.

The hospital course was extremely complicated, but was dominated by rapidly progressive renal insufficiency with a creatinine level rising from 3.7 mg per dl in July to 10.1 mg per dl at the end of August. A renal arteriogram was done and showed small smooth kidneys without microaneurysms. An open renal biopsy was carried out after a percutaneous biopsy yielded inadequate tissue. Examination of the biopsy specimen showed amyloidosis with primary involvement of the arterial walls and the mesangial areas of the glomeruli. Immunofluorescence showed positive staining of the amyloid material with anti-kappa light chain serum. Workup of the amyloidosis included a serum protein electrophoresis; all studies were negative for M components.

On August 23, during an attempt to place a Scribner shunt under general anesthesia, ventricular tachycardia and ventricular fibrillation developed, requiring that cardiopulmonary resuscitation be carried out. Postarrest in the coronary care unit, the patient's creatine phosphokinase was positive for the myocardial isoenzyme (MB band). An echocardiogram at that time showed small chambers, low stroke volume and thickened ventricular walls. A Scribner shunt was placed under local anesthesia, and hemodialysis successfully undertaken. Gastrointestinal workup consisted of an upper gastrointestinal series with a cineesophagogram showing a notably atonic and dilated distal esophagus with poor gastric and small bowel motility. Evaluation of the enlarged thyroid disclosed normal thyroid function, normal calcitonin values, normal antithyroid antibody levels and a low thyroid-stimulating hormone value. Thyroid scan showed an enlarged, irregularly labelled gland. Based on experimental studies of amyloidosis, the patient was begun on a regimen of colchicine, 1 mg by mouth three times a day, in an attempt to alter the progression of disease.

The patient was discharged on hospital day 37 and the diagnoses at that time were (1) primary amyloidosis, (2) end-stage renal failure secondary to amyloidosis, (3) progressive cardiomyopathy also secondary to amyloidosis, (4) gastrointestinal hypomotility, secondary to amyloid and (5) diffuse goiter of unknown cause. Arrangements were made for the patient to receive continued hemodialysis as an outpatient. However, during the patient's first postdischarge dialysis, a cardiac arrest occurred after she became hypotensive. Resuscitation attempts were not successful. An autopsy, carried out by the Oakland coroner, showed amyloidosis of the thyroid gland, the distal esophagus, the interstitium of the lung, the spleen, the liver and the kidney, and diffuse amyloid of the myocardium. The primary cause of death was cardiorespiratory failure due to amyloidosis.

DR. SMITH: *We are very pleased to call on Dr. Wallace V. Epstein to discuss this case and this general topic of amyloidosis. In view of Dr. Epstein's long interest in this area, we would like to ask him a few simple questions. We would like to know what is this starch-like material called amyloid? Why is it deposited in the tissues? What kinds of syndromes result? Finally, is there anything that can be done therapeutically in such cases?*

DR. EPSTEIN:* This patient's tragic story raises a group of clinical, immunological, therapeutic, and even economic and bioethical questions. I take these up in turn.

There is no discrete entity of amyloidosis, and there is no single amyloid substance. The generic term amyloid encompasses a variety of substances, all of which appear as homogeneous, eosinophilic, extracellular deposits by light microscopy. Under polarizing microscopy with Congo red staining they display green birefringence. By x-ray diffraction they show a beta pleated configuration, and by electron microscopy they consist of fibrils with

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a diameter of 100 angstroms. Amyloidosis is probably the first disease, or group of diseases, recognized as caused by configurational change in the protein of origin. The ultrastructure of amyloid consists of side-by-side amino acid chains linked by hydroxyl bands (beta structure) with the amino terminus of the chains facing in opposite directions (antiparallel). It is this antiparallel, beta pleated structure that explains the insolubility of the substance, its relative resistance to enzymatic degradation, the green birefringence on Congo red staining and probably why amyloid is a very poor antigen.

Amyloid has a long and distinguished middle European history dating to 1846, when iodine was the major stain available to study autopsy material. Indeed, this waxy paraffin-like material infiltrating organs stained with iodine as though it were made of starch; hence, the term amyloid or starch-like. We now know that a rather nonspecific polysaccharide that is anionicly bound with amyloid was responsible for the first staining. The protein nature of amyloid became apparent later. Two sets of observations changed our entire concept of amyloid and moved us into the contemporary era of biochemical and immunologic characterization. The first was Cohen's observation in 1959,[1] using electron microscopy, that all forms of amyloid are made up of rigid, nonbranching fibrils. The second was Glenner's study in 1969,[2] in which solubilization of this amorphous material was accomplished, first by using distilled water, and later using 6-molar guanidine and then mercaptoethanol. This permitted the subunit of amyloid to be dissolved, and for the first time made possible sophisticated chemical and immunological analyses.

The clinical forms of amyloidosis have been classified by the distribution of the deposits, the presence or absence of underlying disease and, more recently, the chemical composition of the amyloid. Table 1 uses the term primary amyloid, the diagnosis we are attributing to this case, implying that the deposit is unrelated to chronic infection (such as tuberculosis, leprosy, or osteomyelitis), to a rheumatic disease or to a malignant condition. Secondary amyloid suggests an association with these diseases as well as with Waldenstrom macroglobulinemia, multiple myeloma, medullary carcinoma of the thyroid or agammaglobulinemia in a very few reported cases. There is also a whole group of other amyloidoses that are of a hereditary nature; familial Mediterranean fever is probably the one with which you are most familiar. It is the only autosomal recessive of the genetic forms of amyloidosis, the others being autosomal dominant. A whole group of organ limited amyloidoses may involve the respiratory tract, urinary tract, conjunctiva, cornea, bone marrow, and senile plaques in the brain. Some amyloidoses are specific to endocrine organs such as medullary carcinoma of the thyroid or amyloidosis of the pancreas. As will be noted subsequently, these endocrine gland amyloidoses may be built of polypeptides secreted by the organs.

Primary amyloidosis and amyloidosis associated with B-lymphocyte neoplasms are of similar

TABLE 1.—*Clinical Classification of Human Amyloid Deposits and Amyloidosis**

SYSTEMIC AMYLOIDOSIS
Plasma cell dyscrasias with amyloidosis
- Monoclonal gammopathy
- Plasma cell myeloma
- Primary (Waldenstrom) macroglobulinemia
- Heavy-chain disease (various types)
- Other neoplasms of the lymphoid system

Agammaglobulinemia with amyloidosis—only a few cases
Secondary amyloidosis
- Chronic suppurative infections, as osteomyelitis, pyelonephritis, etc.
- Chronic inflammatory conditions, as rheumatoid arthritis or inflammatory bowel disease
- Hodgkin disease
- Nonlymphoid solid tumors, particularly renal and gastric adenocarcinoma

Heredofamilial amyloidosis
- Amyloid polyneuropathy: Portuguese, Indiana and Iowa types
- Familial Mediterranean fever
- Amyloid nephropathy with urticaria and deafness (Muckle-Wells)
- Familial cardiac amyloidosis
- Lattice corneal dystrophy, systemic form

ORGAN-LIMITED AMYLOIDOSIS (LOCALIZED)
Probably plasmacellular related (diffuse or nodular)
- Respiratory tract
- Urinary tract
- Conjunctiva, cornea and orbit
- Bone marrow and lymphoid organs

Cardiovascular limited ("senile" cardiac)
Lichen amyloidosus (lichenoid amyloidosis)
"Senile" plaques, brain

LOCALIZED DEPOSITION OF AMYLOID
Endocrine tissue associated
- Medullary carcinoma of thyroid
- Islet cell neoplasm of pancreas
- Islets of Langerhans, pancreas

Calcifying epithelial odontogenic tumor
Laryngeal
Plasmacytoma
Myeloma casts, kidney

*From Glenner G, Page DL: Amyloid, amyloidosis and amyloidogenesis. Int Rev Exp Path 15:1-85, 1976

structural origin and may present with rather similar clinical features. A typical patient with primary amyloidosis would be a person with macroglossia, so-called "pinch purpura" due to infiltration of amyloid in the vessels of the skin allowing easy rupture of the vessel, "shoulder pad" arthropathy, and visceral organs infiltrated by amyloid. Renal disease and cardiac disease are seen in both primary and secondary amyloidosis. The prevalence of the different kinds of amyloidosis varies by time and location. New York Hospital in 1960 reported that 63 percent of cases were of the secondary type, usually due to tuberculosis, but rheumatic diseases have replaced tuberculosis as the most frequent cause of secondary amyloidosis. Over the years, primary amyloidosis and myeloma-associated amyloidosis have increased in relative prevalence; however, the prevalence of particular types depends upon geography. In Israel or Portugal, for example, the hereditary amyloidoses are 40 percent or 50 percent of all cases. A quarter of the patients with seropositive, nodule forming, rheumatoid arthritis have amyloid deposits at autopsy. The most frequent cause of amyloidosis in children is juvenile rheumatoid arthritis. In multiple myeloma, even in those cases with free light chain protein in serum and urine, amyloidosis develops in only 10 percent to 15 percent of patients.

Amyloidosis develops in almost half of all paraplegics, perhaps due to chronic infection and chronic antigenic stimulation. Medullary carcinoma of the thyroid is a tissue diagnosis that requires amyloid deposits be identified; hence, an association of 100 percent. As we age, we seem to have the ability to accumulate fair amounts of amyloid, some say there is a 90 percent prevalence in those over age 70 at autopsy. Horses used for the manufacture of commercial antisera almost all have amyloid deposits in viscera. It therefore appears that amyloid, rather than being a rarity, is something that develops in everyone in small quantities, but in some this develops to clinical significance. The kidney is a common site of amyloid deposit. Renal failure is the most frequent cause of death in patients with amyloidosis, with glomerular amyloid deposition most commonly seen. Tubular atrophy and obstruction are also common manifestations of amyloid, particularly when of the primary or myeloma-associated form.

The discovery of chemical methods to solubilize and characterize amyloid led to the observation that primary and multiple myeloma-associated amyloid consists of the light chain protein of immunoglobulin of either kappa or lambda specificity.[3] As you recall, all immunoglobulins consist of heavy and light polypeptide chains. The immunoglobulin type is determined by the heavy chain composition. The light chain proteins are the same in all of the immunoglobulins, and are bound to heavy chain by both the same hydrogen and covalent bonds. The N-terminal or variable half of light chain bears the antibody binding site, while the C-terminal is the common portion of the light chain. Primary amyloid fibrils are built of the variable half of light chain protein of either kappa or lambda specificity; therefore, primary amyloid, like myeloma-associated amyloid, is monoclonal and can either be of kappa or lambda specificity. The precursor of tissue amyloid probably exists in serum, but we really are not certain how to identify that *amyloidogenic* precursor. Not all light chain protein, whether primary or myeloma-associated, is converted to the fibrillar structure we call amyloid. The building block, the N-terminal half of light chain protein is of a 10,000 dalton size and may or may not be identifiable in the patient's urine or serum. The amyloid designated secondary to tuberculosis, to rheumatoid arthritis, or to other chronic infections or inflammations is composed of a different protein than primary amyloid. The secondary amyloid building block is called A-protein, but it looks the same as primary amyloid on light, polarization and electron microscopy. Its serum precursor is called serum amyloid A (SAA). Serum amyloid A is an acute phase reactant, and is probably synthesized by polymorphonuclear leukocytes.[4] Serum concentrations of SAA have proved to be poorly predictive of the presence of tissue deposited amyloid.

Other possible building blocks from which amyloid fibrils may be fabricated are endocrine gland polypeptides such as insulin, calcitonin and parathyroid hormone. Amyloid fibrils may be made from these *in vitro,* but it is not clear by isolation and sequencing that spontaneous amyloid in the thyroid, or in the pancreas, are actually made of these substances. So, it appears that a number of substances can be converted into the fibrillar material we call amyloid.

With the advent of electron microscopic studies of isolated amyloid, a totally different pentagonal shaped protein, termed P-protein, was identified. P-protein is not seen in the amyloid bearing tissue as it is taken from the patient, but in

the process of extraction and purification, disks of P-protein appear. They are present in both primary and secondary amyloid, and derive from a normal serum protein that can be identified immunologically as an alpha 1 glycoprotein. The fascinating thing about P-protein is that it is a calcium-dependent binding member of the first component of complement designated Clt; thus, enlarging the well known Clq,r,s complex. For those of you whose memory goes back even further, P-protein or serum Clt appears to be identical with what used to be called the acute phase reactant C-reactive protein. It is not clear yet why this additional P-protein absorbs to the amyloid fibril, and why it has a different fibrillar structure, and how all this relates amyloid to the complement system.

Let us return to our patient who is said to have primary amyloidosis. The reason this is less than certain is that unless amyloid tissue is removed, solubilized and characterized, we really do not know that this patient had amyloid of light chain origin. In addition to a statement concerning the structural building block of amyloid, one needs to search intensely for evidence of a monoclonal immunoglobulin, both in serum and urine, since L-chain amyloid is always made from the N-terminal half of a monoclonal light chain. You can see that many characteristics of primary amyloidosis suggest an underlying B-lymphocyte dyscrasia. Dr. Osserman at Columbia in New York feels that in almost all patients with primary amyloid, evidence of a monoclonal M-component in the serum can be shown by immunological techniques.[5]

How does the light chain of immunoglobulin convert to this organ destructive amyloid fibril? If I compress a mass of direct and indirect data, the theory can be summarized as follows: Somewhere in the patient, there is a clone of B-lymphocytes producing either an intact kappa or lambda monoclonal light chain or the N-terminal half of the light chain, each of which is amyloidogenic. That is, something about its makeup allows it to be converted into a fibril. The cell of origin could either be neoplastic or stimulated in response to chronic infection or inflammation. The product of that B-lymphocyte would enter the circulation and because it has a molecular weight of 20,000 or less would pass through the renal glomerulus. It would be resorbed in the proximal tubule and most of it rapidly degraded by lysosomal enzymes, but some may be only partially degraded and return to the circulation. Some light chain may be generated locally at the site of inflammation; that is, there may be a plasmacytoma-like mass of plasma cells at the site of amyloid synthesis rather than the precursor coming from distant sites. That precursor material is then processed locally by macrophages into amyloid fibrils. The fibrils are thought to form in the cell and are then released into the surrounding tissue. This is a jigsaw puzzle and I have thrown in a few pieces that are more speculative than established.

A word of review about light chain protein physiology. Normally our B-lymphocytes manufacture intact immunoglobulins, but as they do so they fabricate almost as much extra free light chain as immunoglobulin. This free light chain protein is promptly filtered at the glomerulus and 60 percent of the intravascular pool is metabolized per hour by the renal tubule cell, a very rapid turnover. This is perfectly normal, and happens to both kappa and lambda chain, and very little, about 3 mg per 24 hours, comes out, intact, in the urine. Almost any injury to the renal proximal tubule such as cadmium poisoning, or systemic lupus erythematosus, damages this ability to degrade filtered L-chain and L-chain proteinuria results. The light chain of normal urine contains about equal amounts of kappa and lambda types. In a person with a monoclonal source, the urine would contain more of one antigenic type than the other. There is almost no literature on the role of the kidney in the processing of monoclonal light chain on its way to becoming an amyloid fiber, but this seems to me a very vital step in that synthetic process. The precursor is next observed in a monocytoid cell. In the studies of Drs. Dorthea Zucker and Edward Franklin, we have learned that the L-chain fibrils appear within the cytoplasm of cells around the amyloid.[6] The great debate is whether this cell is ingesting the fibrils and degrading them, or synthesizing and releasing them, or whether both events are occurring. A similar sort of controversy exists concerning collagen fibrils, and whether the procollagen fibrils are assembled in the cytoplasm of the fibroblasts before release. In any case, our current thinking is that through some stimulus, B-lymphocytes convert to plasma cells and release light chain. Another possibility is that antigen-antibody complexes may be the amyloid precursor. Phagocytic cells may process antigen-antibody complex and enzymatically degrade them to light chain fragments. Even less is certain concerning amyloids built of non-L-chain protein.

How can we explain the fact that amyloid has been shown to develop in both anergic persons and agammaglobulinemic persons? It is thought that persons in whom amyloid develops are subject to an antigenic stimulus greater than their capacity to handle. Persons with tuberculosis or with leprosy have an immense antigenic stimulus, but an agammaglobulinemic or anergic person may also have an antigenic load greater than their capacity to handle. Thus, one explanation is that there is a deficiency in antibody processing relative to the antigenic load. Others feel that the abnormality is in the cell; there is an abnormality, perhaps genetic in some, to process antigen and antibody complexes and to degrade them completely. Degrading the light chain molecule to half molecules allows the possibility of assembling amyloid fibrils. It has been shown that if monoclonal urine light chain protein, and here the old term Bence Jones protein is applicable, is treated with acid and pepsin *in vitro* a precipitate results, which on electron microscopy reveals amyloid fibrils.[7] This observation led my coworker Mrs. Tan and me to examine a series of renal lysosomal enzymes acting on kappa and lambda light chain proteins.[8] We found the same amyloid-like fibrils in the resulting precipitated material. Therefore, using normal renal enzymes at a physiological pH, we were able to show fibril formation with a Congo red positive reaction having the typical structure of amyloid on electron microscopy. On x-ray diffraction it was also shown to conform to amyloid fibril characteristics. Interestingly, if you leave the mass of material in the same enzyme solution, it undergoes dissolution to nontrichloracetic acid (non-TCA) precipitable fragments. This fits with the idea that the same enzyme system may be responsible for both the generation and the enzymatic degradation of the amyloid fibril. Others have produced similar fibrils from insulin.

The current story of the treatment of amyloidosis is sad, indeed. If the amyloid is secondary, you remove the antigenic load; that is, the osteomyelitis or tuberculosis. There have been instances in which the secondary amyloid diminished in liver and spleen with early removal of a localized inflammatory mass. In today's case, we are concerned with primary amyloidosis. Drug damage to the B-lymphocyte population that is producing the amyloidogenic light chain substance has been tried; for example, melphalan has been used.[9] The claims that such therapy makes a difference are weak. There is one disturbing observation of the production of acute leukemia in two of 17 patients who were treated with melphalan. Blockade of the macrophage ingestion and lysosomal action by colchicine has been tried. In experimental models of amyloid formation such as casein treated mice, administration of colchicine has diminished amyloid formation. Colchicine stops the abdominal pain of familial Mediterranean fever, but there is no evidence that it has benefitted persons with well established amyloid disease. Another possible approach is to denature the amyloid protein, perhaps to augment body removal. Penicillamine and dimethyl sulfoxide (DMSO) have been tried without success. In general, treatment of primary amyloidosis has been unsatisfactory. Of the four drugs—melphalan, prednisone, colchicine and penicillamine—none has proved by controlled studies to be efficacious in the treatment of primary amyloidosis. Unfortunately, that is the current state of therapeusis.

I earlier promised to comment on two other points raised by the case discussed today. It was evident on admission that the patient had far advanced myocardial and renal disease and without admission these could have been established as due to amyloidosis. The literature is clear that no therapeutic modalities now available could affect that combination of organ system involvement. Her one month in hospital here generated a bill of $19,275 and she spent essentially all of the last month of her life under intensive medical investigation. Hemodialysis could not have been expected to change any of the inevitable course. I believe these facts raise significant ethical and economic issues that time constraints do not allow me to discuss further.

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Important Advances in Clinical Medicine

Epitomes of Progress—Urology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in urology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Urology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Extracorporeal Corporo-Venous Shunting for Priapism

Priapism is a persistent, painful penile erection unaccompanied by sexual desire. In the past two decades, several methods of treatment have been developed, most of which result in detumescence sooner than if the disease were to run its natural course. Inherent in all shunt procedures is the concept that they are temporary. In view of this and the fact that the potency rate even in treated cases still remains at about 50 percent, a new protocol for the management of idiopathic priapism has been derived at the University of Utah Medical Center.

An initial thorough search for the cause is undertaken, and the primary disease in appropriate cases is treated. If conservative measures fail to produce detumescence, aspiration and irrigation of the corpora with pneumatic cuff compression is initiated. If the priapism persists, a shunt procedure such as extracorporeal corporo-venous shunting is carried out.

The advantages of extracorporeal circulatory management include the relative simplicity, requiring only frequent monitoring to assure that flow is adequate, and the procedure can be repeated in cases of recurrent priapism.

CHARLES L. GATES, MD
RICHARD G. MIDDLETON, MD

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Recent Experience in the Management of Fournier Gangrene

IN REVIEWING our recent experience in managing five cases of necrotizing fasciitis or synergistic gangrene of the scrotal-perineal region, otherwise known as Fournier gangrene, we found ourselves in agreement with current literature as to pathogenesis and bacteriology but in disagreement as to the wide radical debridement advocated.

As the name implies, necrotizing fasciitis spreads rapidly along the fascial planes of the lower abdomen, perineum and perianal region. Obvious progression of erythema, scrotal enlargement and induration extending into the perineum and buttocks occurs in a matter of only several hours. All

of our patients were noted to have crepitus most often of the edematous scrotum which was confirmed by interstitial gas on x-ray studies of the kidney, ureter and bladder.

Systemic diseases such as diabetes mellitus severe atherosclerotic disease often with neurologic deficits may be predisposing factors. Urinary extravasation and periurethral phlegmon may lead to the infection as well. In one of our cases there was a colorectal primary source of infection, with evidence in the literature suggesting an increase in morbidity due to the occult nature of the infection.

Both aerobic and anaerobic cultures were obtained yielding a microaerophilic Streptococcus associated with an aerobic Escherichia coli. These organisms were synergistic with mixed aerobic choliforms such as Bacteroides species, Fusobacterium and Peptostreptococcus. Chloramphenicol and high dose aqueous penicillin G is the preferred treatment.

With experience our surgical approach became more conservative for questionable areas of viability. Rather than the wide radical debridement advocated by Persky, efforts were directed in excising only obvious necrotic tissue and leaving edematous tissue that bled poorly for later demarcation. We found that adequate aeration and drainage would salvage needed tissue for later closure that provided a quite satisfactory cosmetic result.

GEORGE GETTY, MD

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Surgical Treat for the Undescended Testis

TESTICULAR BIOPSY STUDIES of several hundred boys with unilateral undescended testis have shown that the scrotal testis begins a process of maturation after 1 or 2 years of age. The undescended testis lags behind its scrotal mate in this maturation process. These anatomic findings have led to the recommendation for orchiopexy at an early age. Many surgeons would now recommend that surgical therapy be done by the age of 2 years.

In addition to placing the testis in its optimum anatomic location for maturation, there may be some benefit in terms of subsequent malignant tumor formation. Among some 220 case reports of testicular tumors developing after orchiopexy, only six cases occurred in children treated by orchiopexy under the age of 10 years. This is suggestive but not proof that early orchiopexy may protect against some subsequent malignant degeneration.

DONALD C. MARTIN, MD

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Martin DC, Menck HR: The undescended testes: Management after puberty. Urol 114:77-79, Jul 1975

Pelvic Radiation Therapy for Localized Carcinoma of the Prostate

SINCE 1965 a total of 432 patients with localized prostate cancer have received intensive local radiation therapy at The Virginia Mason Medical Center, Seattle. A study group of 277 patients, treated from 1965 through 1975, included 221 with stage C cancer, 36 with stage B cancer and 10 with diffuse stage A disease.

Following careful pretreatment evaluation and treatment planning procedures, the patients received external beam radiation therapy to a level of 6,500 to 7,000 rad. Though initially using cobalt 60, current treatment techniques employ a 10 mv linear accelerator photon beam with an arrangement of opposing anterior and posterior and bilateral pelvic fields, supplemented with more localized bilateral arc rotation boost therapy. Particular attention is directed to gastrointestinal tract shielding.

The five-year survival of the stage C group was 57.7 percent, with no apparent survival influence related to use of estrogen therapy. The 25 patients with postprostatectomy residual or recurrent cancer were treated more cautiously, but tolerated the treatment well with eight of 12 eligible patients surviving five years.

Increasing acceptance of local intensive radiation therapy in the management of prostate cancer is supported by increasing the referral of patients with stage BII and C cancer. Our series of patients has tolerated treatment with acceptable morbidity and with greater maintenance of sexual potency.

Multiple reports attest to the apparent value of external radiation therapy in local management of prostate cancer. Therefore, until more effective methods of treatment are conclusively shown, there is justification to continue its use in: the management of locally advanced nonresectable

stage C cancer; selected cases of potentially aggressive stage A disease; patients with high grade diffuse and bilobular stage B cancer; and patients who have residual or recurrent cancer after radical prostatectomy or trials of estrogen therapy.

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Long-Term Indwelling Foley Decatheterization and Bladder Rehabilitation In Spinal Injury Patients

IN 40 MEN with spinal injuries whose mean age was 41.4 years (range 22 to 68), indwelling catheters had been in place for a mean period of 7.6 years (range 1 to 24) following spinal injury. There were 21 tetraplegics, 14 paraplegics and 5 with cauda equina lesions (all clinically complete lesions). All presented for urodynamic evaluation and possible removal of indwelling catheters. All patients had long-standing urinary tract infections. All tetraplegics and high paraplegics had varying degrees of autonomic dysreflexia. After hospital admission, intermittent catheterization was started on all patients; however, tetraplegic patients with previous history of autonomic dysreflexia were also given anticholinergics to reduce frequency of catheterization. Urinary tract infection was controlled with an appropriate antibiotic, and bladder irrigations with neosporin genitourinary irrigant solution. Cystomanometry, sphincter electromyography, urethral pressure profile and voiding cystourethrographic studies were done only after patients had been on intermittent catheterization for a minimum period of 48 hours but usually after seven days. There were 12 patients (30 percent) in whom vesicoureteral reflux was noted (possibly indwelling catheter had been left in due to reflux). Eight patients (20 percent) had been treated for bladder and renal stones on several occasions. In 18 patients simultaneous cystomanometry and periurethral striated electromyography showed detrusor-sphincter dyssynergia.

Indications for transurethral extended sphincterotomy in this group of patients included the following: (1) detrusor-sphincter dyssynergia, (2) vesicoureteral reflux, (3) inability to open bladder neck and posterior urethra on voiding cystourethrography. In 33 patients transurethral sphincterotomy was done. There were seven patients in whom transurethral sphincterotomy was repeated because high residual urine persisted. No surgical operations were done in seven patients; in three in this group it was recommended, but patients deferred surgical therapy. Follow-up (six months to four years) shows pronounced improvement in general well-being, no recurrence of bladder stones, amelioration of autonomic dysreflexia and notable improvement in vesicoureteral reflux. At the last follow-up, there were positive urine cultures in six patients (15 percent). All patients were receiving prophylactic medications, either trimethoprim/sulfamethoxazole (Septra) or methenamine mandelate (Mandelamine) and ascorbic acid.

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Conservative Treatment of Early Carcinoma of the Prostate: Comparison of Patients Less Than 70 Years Old With Those 70 or Older

A RETROSPECTIVE COMPUTERIZED STUDY was made of 155 patients first seen between 1930 and 1967 with early (stages A and B) prostatic carcinoma in whom endocrine therapy, either immediate or delayed, had been carried out. The patients were divided into two groups: (1) Patients less than 70 years old when the first diagnosis of carcinoma was made and (2) those 70 years old or older. The crude 10-year or longer survival rate of group 1 (66 percent) was only slightly less than the expected survival rate (71 percent) of that age group (mean age 60 years) but there was a significantly greater difference in the survival rate in the 15-year or longer (42 percent versus 54 percent) and the 20-year or longer (23 percent versus 35 percent) periods. The crude 10-year or longer survival rate of group 2 (70 years old or older) was 37 percent (expected survival, age 78, was 25 percent). The crude 15-year or longer survival rate (16 percent) and 20-year or longer survival rate (7 percent) was also better than the expected survival (7 percent 15-year and 1 percent 20-year).

Probable explanations for the crude survival

rate of this group being better than the expected survival rate are as follows: (1) These were all private patients and were in better health than the same group in the general population and (2) they were examined at six-month to one-year intervals and any other medical problems were taken care of as they arose. Other reports have shown a better survival rate in elderly patients with early carcinoma of the prostate than in their comparison population. It is evident from these data that endocrine therapy, either immediate or delayed, is preferable for men 70 years or older who have early prostatic cancer.

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Prostate Carcinoma/Therapeutic Considerations in the Management of Gross Lymph Node Metastases

PRIMARY PROSTATE CARCINOMA can usually be controlled by megavoltage radiotherapy. Unfortunately, in many patients so treated, distant metastases later occur. The percentage of distant mestastases has paralleled the expected incidence of lymph node metastases. In recent years, surgical and radiotherapeutic efforts have been expanded to include the treatment of the lymph nodes. In some patients with minimal spread, control has been achieved. In most patients with gross lymph node metastases distant metastases continue to develop. Probably neither therapeutic approach alone can effectively eradicate extensive lymph node metastases. Surgical therapy cannot encompass all lymph node disease. Radiotherapy directed to the lymph nodes is limited to 5,000 rads because of small intestine tolerance. While this dosage can sterilize micrometastases, it cannot be expected to sterilize gross lymph node metastases. If the disease in the lymph nodes is comparable to the primary tumor, dosages of 6,000 to 7,000 rads would be needed.

For the past eight years we have explored the use of estrogens and megavoltage irradiation in the management of patients with gross lymph node metastases. The diagnosis of gross lymph node metastases was made by lymphangiography or selective lymph node biopsy. The usual lymphangiogram criteria for detection of lymph node metastases was not used because it has been shown to be inaccurate. Only patients with notably enlarged lymph nodes and abnormal lymph node architecture were included in the study. Estrogens were systematically given two months before radiotherapy and continued throughout radiotherapy. All patients received megavoltage radiotherapy to the primary tumor, pelvic and periaortic lymph nodes. The primary tumor received 6,500 rads and the pelvic and periaortic nodes 4,800 rads. In order to assess response to treatment, therapy with estrogens was discontinued within one year of completion of irradiation. The treatment regimen was well tolerated.

By using serial x-ray studies following lymphangiograms and serial computerized axial tomograms, we observed that estrogens can significantly reduce the tumor burden in lymph nodes. This may render radiation more effective at the modest and safe dosages that can be delivered. Following completion of radiotherapy, (18 of 25 patients) 72 percent of patients with gross lymph node metastases have remained free of disease. Follow-up computerized axial tomographic scans done at one and two years showed persistent favorable lymph node response. Eight percent are alive with disease. Twelve percent died from disease. Eight percent have been lost to follow-up. Our favorable results may be tempered as more patients are studied and followed longer. The experience does suggest that this treatment regimen can produce long periods of disease-free survival. The potential for cure exists.

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Orchiectomy After Presumed Estrogen Failure In Treatment of Carcinoma of the Prostate

TO REASSESS the value of bilateral orchiectomy in reversing the progressive spread and pain in those patients with carcinoma of the prostate who had previously responded well to estrogen therapy, we

selected for study 29 consecutive patients who showed signs and symptoms of "breaking through" hormonal control. These were chosen from a total of 640 patients with proven carcinoma of the prostate.

A retrospective review of these 29 patients disclosed that pain developed in 19 of them. There were genitourinary complaints in nine patients, generalized fatigue and weakness in five, and rectal complaints in two. Before orchiectomy there were objective findings in all of them consistent with stage D carcinoma of the prostate; that is, bony and soft tissue metastases. In 18 there were either elevated acid and alkaline phosphatase levels or abnormalities of other blood monitors. In five an enlarging prostatic mass was found to have developed despite estrogen therapy.

Practically, the decision to do an orchiectomy depended primarily on the subjective deterioration in a patient's condition during treatment with estrogens and our assessment of the patient's response to orchiectomy has been based usually on the degree of symptomatic relief. However, in five of the 29 patients there were objective responses manifested by either reduction of elevated blood monitors, recession of soft tissue metastases or palpable diminution of prostatic mass. Of the 29 patients, there had been response in 11 for more than six months, response in 10 of up to six months and no response in eight. A comparison of the known life spans after orchiectomy of the three groups correlated well with the patient's subjective and objective responses. These results seem to justify bilateral orchiectomy after failure of continuous response to estrogen therapy in carcinoma of the prostate.

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EDITORIALS

Of WAMIs and AHECs

ELSEWHERE in this issue is a report of the impressive success of the WAMI program of the University of Washington School of Medicine in Seattle. Begun with federal funds it is now entirely supported by the legislatures of the states of Washington, Alaska, Montana and Idaho (WAMI). This huge area is more than a fifth of the land area of the United States, and is mostly underserved by physicians and other health professionals. The distances are formidable, as is at times the weather. But in spite of all the difficulties an effective educational network has been created and is fulfilling its goals.

A similar approach, though on far less grand a scale, is underway in the Central San Joaquin Valley of California in the federally sponsored Area Health Education Center (AHEC) program of the University of California, San Francisco. There also it can be shown that educational programs involving medical students, residents and practicing physicians can bring physicans and other health professionals to underserved areas to ease health manpower shortages, and thus enhance both access to health care and its quality.

In programs such as these a real solution to the problem of maldistribution of physicians and other health manpower seems to be emerging. It turns out to be a multipronged approach, which both serves the needs of medical schools and health science centers for off-campus training sites —particularly for family practice and primary care—and the needs of government which is committed to improving access and quality of care in underserved areas by recruiting and training professionals to serve in these areas. Family practice and primary care turn out to be a natural and needed focus around which training sites can be developed for student and resident physicians as well as other health professionals. Young professionals are introduced to the areas and trained there, and a professional base is created to which they can relate even after entering practice. Continuing education of good quality is developed which also helps to overcome the sense of professional isolation that is so often a deterrent to practice in underserved areas. And a not to be overlooked benefit is that the faculty from the supporting science centers get out of their ivory towers to supervise the educational experiences of students and residents, and in so doing become familiar with local practice problems and contribute significantly to continuing education and quality of care.

This package appears to provide an effective solution to the health manpower maldistribution problem and a way to improve health care. It can now be shown that as the primary care educational centers develop in medically underserved areas, with oversight from a major health science center, students and residents seek training in these areas and eventually tend to remain to practice in them. A kind of collegiality develops among practitioners and with the health science centers which has the effect of negating profcssional isolation. Educational goals for primary care and social goals for better access and better quality of care through better distribution of health manpower are both well served. Legislative support for these kinds of programs is clearly in the public interest and makes possible an educational and practice network which can solve what has been a most vexing problem.

We congratulate the University of Washington and the WAMI states on the obvious success of their pioneering effort.

—MSMW

Prolonged Thoracic-Duct Drainage in Rheumatoid Arthritis and Systemic Lupus Erythematosus

GOWAN'S PIONEERING WORK in rats showed that one can deplete the entire lymphoid apparatus by thoracic-duct drainage. With this he produced an immunodeficiency evident in both cellular and humoral responses to antigenic stimulation. Lymphopenia was seen in the blood, spleen, lymph nodes, Peyer patches and other sites of lymphocytic collection in the body. During the middle and late 1960's, there were a few sporadic reports from clinical investigators showing that man too could be rendered immunodeficient by this

technique, with focus on effects in patients with glomerulonephritis, rheumatoid arthritis and renal transplantation. More recently, myasthenia gravis and systemic lupus erythematosus have also come under investigation. The UCLA Interdepartmental Clinical Case Conference presented elsewhere in this issue summarizes several years of experience in that institution with prolonged thoracic-duct drainage in a number of patients with rheumatoid arthritis and in two patients with systemic lupus erythematosus.

The UCLA experience is superior to others previously published; the investigators in that institution achieved a technical proficiency that allowed them to keep thoracic-duct drainage going over many weeks, each day returning the humoral elements of the lymph to the patient by intravenous infusion. Changes in immunologic function and manifestations of disease could, therefore, reasonably be attributed to the lymphoid cell loss in the patients. This study presents us with the most nearly definitive data yet developed that rheumatoid arthritis is an immunological disease. The study does not tell us, however, the relative importance of T cells or B cells in the process.

One of the terrible burdens borne by clinical investigators is the difficulty of developing adequate controls for their observations of patients. Sometimes, as in this study of thoracic-duct drainage, truly adequate controls can never be developed. Consequently, although the reported improvement of patients with rheumatoid arthritis in all reported studies of thoracic-duct drainage is very impressive, all those who know rheumatoid arthritis know the importance of suggestion as a placebo effect and of hospital admission alone as a therapeutic effect in the disease. Dr. Paulus and his colleagues are well aware of these effects and have done their best to cope with them. The difficulty is well illustrated by their need to resort in one phase of their report to the clinical course shown by their patients during previous hospital stays, for entirely different purposes, as the control for the same patients now in hospital for thoracic-duct drainage. Nor is the presentation of the clinical course of a patient who did not have a successful thoracic-duct drainage a truly adequate control for those who did have the drainage successfully instituted. But we are men, not mice, so a true sham-operated control, double-blinded for evaluation, is obviously impossible, and again the UCLA group have done the best that they could.

The casual observer might be most impressed by the reported exacerbation of clinical manifestations of disease after reinfusion, intravenously or intraarticularly, of live thoracic-duct lymphocytes into patients, whereas injected dead cells did not cause exacerbation. One major technical deficiency in these observations is that a further control is needed beyond that of the dead cells. It should have been shown that live cells from a haplotype-identical normal donor (a first-degree relative would have a reasonable likelihood of providing such cells) also did not cause appearance of clinical symptoms. There is also a theoretical problem: We need to understand why the cells from a single day's thoracic-duct drainage given intravenously to patients generally exacerbated their symptoms promptly. while clinical manifestations of disease generally did not reassert themselves until weeks after discontinuation of thoracic-duct drainage. It seems unlikely that it takes several weeks for the thoracic duct to begin to deliver its full complement of lymphoid cells to the blood again; but, if this is so, these investigators have failed to demonstrate that to us.

Despite these difficulties, the UCLA experience is impressive and important. The most striking and convincing findings were of the degree of immunodeficiency induced in their patients, most vividly displayed in the induction of prolonged tolerance to skin grafting. If, in fact, prolonged thoracic-duct drainage can be developed to the point at which it can with reasonable frequency allow the induction of immunological tolerance in man, a wide range of new therapeutic possibilities could be opened up.

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Can GIGO Be Eliminated?

ONE OF THE most pressing unsolved problems in today's society is how to deal with the great social, economic and political complexity that is the product of scientific and technologic progress. The problems related to this complexity are worldwide, but are particularly troublesome in the more advanced industrial nations, and even more so in so complex an enterprise as health care in this nation. The problems are probably the most obvious in America where they are certainly evident in medicine and health care. There are two easily

discernible efforts to deal with this complexity; both in a way strike at the heart of the American system and our way of life.

A basic difficulty seems to be that as our science progresses and the new knowledge is applied in an increasingly interdependent technologic society, the number of bits and pieces that have to be dealt with, and the ways they must relate to one another if things are to run smoothly, increases exponentially. The response of science and technology to this has been to develop computers which can process bits (or bytes) of data with astonishing speed and absolute accuracy. But computers can do only what they are programmed to do—no more, no less. In computer parlance *GIGO* means "garbage in, garbage out," which is to say that a computer has no way of addressing a problem except in the fashion it has been programmed. Computers are useful, even essential, in modern society, but they are insensitive and inanimate, and to the extent they touch people's lives, as with computerized personal financial or health data for example, they know not what they are doing.

Government in all its branches, and particularly the federal government, has been overwhelmed by all these new technologic, social, economic and political bits and pieces, and the ways they must relate to one another. In our system we elect our lawmakers and other officials, expecting them to see that things run smoothly with as little interference in our daily lives as possible. But the time has long since passed when the constitutionally appointed officers can do all this themselves. The time is simply not available. There is more to be done than any one person can do. Their answer has been to proliferate large and, in the case of the Congress, sometimes huge staffs of professional and clerical assistants (paid by the taxpayers) whose function is really to do the work for the duly elected or appointed officials, who in turn must necessarily be guided by the advice of their assistants when they speak or act. Many of these advisors are bright, energetic and ambitious young persons fresh from college or professional school. Others are professional government bureaucrats. In both cases the advisors usually have little or no firsthand knowledge or experience with the problems to be dealt with. Thus it turns out that more and more of our constitutionally chosen government officials are being programmed by staff who for these reasons may be relatively insensitive to the nature of real problems as they actually exist or to the significant human factors involved which are inherent in them. Certainly we are seeing more and more GIGO in the activities of all branches of our government.

It is unlikely that GIGO can ever be completely eliminated, but if something could be done to increase the sensitivity and the real knowledge (as distinct from conceptual or theoretical knowledge) of the programmers, whether of computers or of government, GIGO might be at least lessened. In the health care field this might be more likely to happen if knowledgeable physicians and other health professionals, as well as knowledgeable members of the public, were more often involved in both the planning and the decision-making process. The programs in the health field, as a result, would much more likely be more responsive to real needs and be more workable. Consensus rather than control would become more the order of the day. And this would tend to enhance rather than erode the American system and way of life.

—MSMW

Happiness Hormone?

EVERY PHYSICIAN knows that some of his patients accept pain without a whimper, while others will cry out at a pin prick. For the removal of a wart one person will need only a few drops of procaine hydrochloride (Novocain), others will need a syringeful. Some obstetrical patients will allow us to make an episiotomy incision and its repair with little or no anesthesia, while others will tense up at the touch of a finger.

We have usually passed this off by saying "It's all in their head." But now Dr. Choh Hao Li, Director of the Hormone Research Laboratory of the University of California in San Francisco, has given us reason to believe that this off-hand remark may come very close to being scientifically correct. He has shown that the pituitary gland, that tiny dynamo that sits there in the sella turcica, unnoticed and unappreciated by most of us, produces varying quantities of a powerful pain-relieving and pain-preventing hormone. He has named the substance beta-endorphin.

If this taxes our credulity, seeming just a bit too good to be true, let us be reminded that C. H. Li and his co-workers discovered adrenocorticotro-

pic hormone (ACTH). More than that, Li has identified the parent pituitary hormone, beta-lipotropin, along with its 91 amino acids from which beta-endorphin is derived. You might say this fellow knows his way around the pituitary.

All this did not happen overnight. Actually it took more than 14 years, and the careful chemical analysis of the pituitary glands of some 500 obliging camels. We are not told why Li chose camels, but we do know that beta-endorphin reaches the specific pain receptors through the spinal fluid pathway. Quite obviously, the length of a camel's spinal column would require a prodigious pituitary pump.

Moreover, the identification of this endorphin was possible only after all the amino acids in the beta-lipotropin chain had been isolated and labeled. Then the peptide fragment of the amino acids 61 through 91 could be identified as beta-endorphin. To a fellow who luckily did not have to depend on his grades in physical chemistry to graduate from medical school, and who today could not tell a peptide from Pepto-Bismol, this sort of chemical wizardry seems almost beyond belief.

It did not take Li and his colleagues long to synthesize this camel pituitary peptide in the laboratory and to show that this substance had an opiate-like activity many times stronger than morphine. Li and his co-workers promptly put this new information to a practical use. They injected their synthetic endorphin into morphine addicts in Taipei, Taiwan, and into methadone abusers in Los Angeles, with surprising results. After one, or at most two, injections of the chemical every person in both groups lost the desire, or the need, for any more narcotics. And, amazingly, the treatment appeared to have a lasting effectiveness; just why is as yet unexplained. Doctor Li suggests that beta-endorphin, when it reaches the opiate receptor sites, may just "sit there" blocking the further need for narcotics.

If all this is true, we wonder why we are not treating all addicts with beta-endorphin. Probably because we do not have that many available camels to supply us with the natural product, or because the laboratory-produced synthetic chemical costs $300 a milligram. The ingenuity of the American pharmaceutical industry will undoubtedly find ways to solve this problem, if the Food and Drug Administration will let it.

It is obvious that there may be a wide range of implications in this beta-endorphin story. Workers in pain relief, among them Dr. Terrence Murphy, of the Department of Anesthesia of the University of Washington School of Medicine, conjecture that these substances could be the reason why acupuncture occasionally is successful. It is postulated that needle manipulation could send an electrical impulse to the brain, causing the production of the necessary pain-preventing hormone, beta-endorphin. Dr. Li goes so far as to surmise that this amazing peptide may turn out to be the "happiness hormone." He made this observation after seeing what happened when a feisty laboratory tomcat was given a small dose of beta-endorphin. Old Tom and a laboratory mouse, sharing the same cage, lived together in peaceful fellowship.

Our ancestral physicians wrote about the importance of body *humours* in sickness and in health. They contended that the fluctuation in our *vapours* and *humours* determined whether our minds and bodies would have radiant health or be afflicted by disease; whether we would live in a state of depression, euphoria or dysphoria; whether we would be stoics or hypochondriacs.

"Nonsense," modern physicians said; "totally lacking scientific substantiation." But substitute *hormones* for *humours* and we may have to concede that our medical forefathers knew through intuition what our fellow scientists may now be revealing to us through their laboratory research.

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CASE REPORTS

Refer to: Levin EN, Hirschfeld DS, Hersch RA: Pericarditis in association with ulcerative colitis. West J Med 130:369-370, Apr 1979

Pericarditis in Association With Ulcerative Colitis

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INFLAMMATION of the pericardium may be present in a variety of systemic illnesses.[1] Seven cases of pericarditis seen in association with inflammatory bowel disease have previously been reported.[2-5] In only two of these was the onset of pericarditis temporally related to the diagnosis of bowel disease. We report cases of two patients in whom pericarditis and ulcerative colitis were simultaneously diagnosed and in whom pericarditis may have been a presenting symptom of ulcerative colitis.

Reports of Cases

CASE 1. A 12-year-old white girl was admitted to hospital on March 20, 1972, with a two-week history of fever and bloody diarrhea. She said she had had no chest pain; however, a pericardial friction rub was noted. Findings on roentgenogram of the chest suggested a pericardial effusion, and an electrocardiogram showed abnormalities consistent with pericarditis (Figure 1). Cultures of a stool specimen grew no pathogens, and multiple studies of stool specimens gave negative results for ova and parasites. A fluorescent antinuclear antibody titer was normal. Sigmoidoscopy showed an erythematous, cobblestoned and friable mucosa compatible with acute ulcerative colitis. Because of a progressively enlarging cardiac silhouette, the patient was given 20 mg of prednisone per day. The cardiac silhouette subsequently decreased in size. She was discharged from the hospital on April 19, 1972. Administration of prednisone was discontinued two months following discharge. On February 23, 1973 she was readmitted to hospital because of fever and chest pain of five days' duration. Radiographic examination showed an enlarged cardiac silhouette and a left pleural effusion. No friction rub was noted. Daily administration of 40 mg of prednisone resulted in rapid amelioration of symptoms. Several subsequent attempts to discontinue prednisone therapy were unsuccessful. Recurrence of bloody diarrhea on November 12, 1973 necessitated treatment with salicylazosulfapyridine and steroid enemas. In June 1975, severe diarrhea again recurred and was poorly responsive to medical management. A total proctocolectomy with an ileostomy was done on July 13, 1975. Following colectomy, episodes of chest pain occurred intermittently and were successfully treated with indomethacin. She has been free of symptoms since July 2, 1976.

CASE 2. A 24-year-old white man was admitted to hospital on April 5, 1976, with complaint of chest pain. Ten weeks earlier he had had onset of tenesmus and bloody stools. Five weeks before admission he noted malaise, myalgias and aching in his chest. Five days before admission chest pains intensified. A pericardial friction rub was present. There were no stigmata of pericardial tamponade. Roentgenogram of the chest showed enlargement of the cardiac silhouette. An echocardiogram showed a large pericardial effusion (Figure 2). A pericardiocentesis was done with the finding of sterile serosanguinous fluid containing 2,500 leukocytes and 4,000 red blood cells per cu mm. The leukocyte determination showed 66 percent lymphocytes and 34 percent polymorphonuclear cells. The protein content was 4.6 grams per dl. Sigmoidoscopy showed friable, granular mucosa. Findings of examination of a rectal biopsy specimen were consistent with ulcerative colitis. Results of skin tests for tuberculosis, histoplasmosis and coccidioidomycosis were negative. Results of tests on acute-phase and convalescent-phase sera for Coxsackie virus and adenovirus were negative, as were results of a mononucleosis spot test, lupus induction test and latex fixation test. On the fifth hospital day, 12 mm of pulsus paradoxus was noted. After aspirin, salicylazosulfapyridine and hydrocortisone enemas were administered, radiographic and echo-

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cardiographic examinations showed resolution of the pericardial effusion; chest pain disappeared. Following discharge, chest pain recurred and treatment was carried out with prednisone, which was discontinued on September 30, 1976. He has remained free of symptoms.

Discussion

Inflammatory bowel disease may have a variety of extraintestinal manifestations including involvement of the joints, skin and biliary system.[6-9] The association of pericarditis and inflammatory bowel disease had been reported in 11 previous cases;[2-5,10,11] in four of these, only brief reference to pericarditis[10] or carditis[11] was made. Of the seven cases reported in detail,[2-5] in two there was simultaneous or nearly simultaneous onset of evidence of inflammatory bowel disease and pericarditis, while in five there was an interval of three to six years between recognition of the two diseases. In four of these five, inflammatory bowel disease preceded pericarditis. In both our patients, onset of pericarditis and onset of ulcerative colitis had occurred within five weeks, thereby strengthening the argument for a causal relationship between the two diseases.

Pericarditis seen in association with inflammatory bowel disease may be relapsing. This was true in two previously reported cases[2,4] and in our case 1. In our patient, colectomy appears to have been curative for both diseases. In the seven previously reported cases, other extracardiac manifestations of inflammatory bowel disease were common, including arthritis in three and skin lesions in five. These manifestations have so far been absent in our two patients.

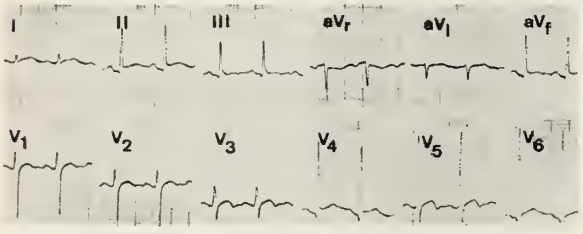

Figure 1.—Electrocardiogram in case 1 showing PR depression, ST elevation and T wave inversion characteristic of pericarditis.

In one of the previously reported cases,[3] tamponade was described. We have seen a 62-year-old man, in whom no cause for pericarditis could be found, who presented in tamponade requiring pericardiectomy. In his case, ulcerative colitis had been diagnosed 24 years earlier and had subsequently remained quiescent. We have not included this case with the two others because of the long interval between onset of bowel disease and onset of pericarditis, which we feel increases the likelihood that in this patient the two diseases were unrelated.

Summary

Percarditis and ulcerative colitis were simultaneously diagnosed in each of two patients. In neither patient could a cause for pericarditis be identified. It is suggested that pericarditis may have been a presenting symptom of inflammatory bowel disease. Recurring pericarditis in one patient appears to have been cured by colectomy.

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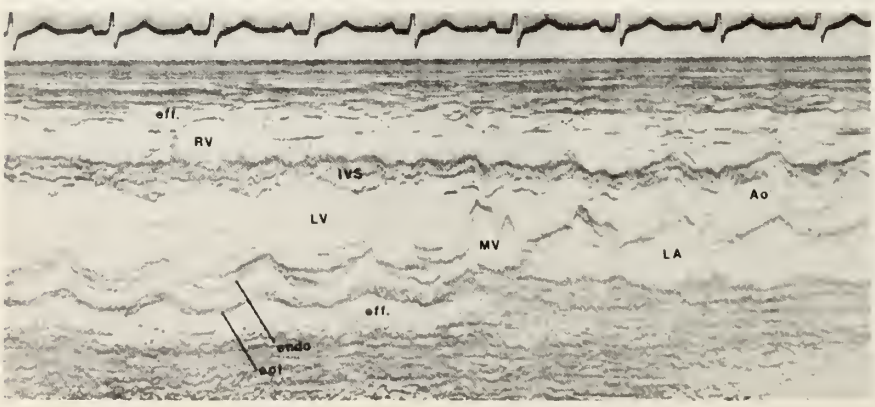

Figure 2.—Echocardiogram in case 2 showing pericardial effusion. Note obliteration of the effusion as the echo beam is swept cephalad toward the left atrium (left to right). Ao = aorta; eff = effusion; endo = endocardium; epi = epicardium; IVS = intraventricular septum; LA = left atrium; LV = left ventricle; MV = mitral valve; RV = right ventricle.

Refer to: Nerenberg L, Crain L: Pulmonary sequestration—A diagnostic consideration in nonresolving pneumonias in young adults. West J Med 130:371-374, Apr 1979

Pulmonary Sequestration

A Diagnostic Consideration in Nonresolving Pneumonias in Young Adults

LEWIS NERENBERG, MD
LUCY CRAIN, MD
San Francisco

PULMONARY SEQUESTRATION is a congenital malformation which is an uncommon cause of nonresolving or recurrent pneumonia. Of approximately 300 previously reported cases, 70 percent to 85 percent have been of the intralobar type, and more than half of the patients have been over 20 years of age when the diagnosis was made. Extralobar sequestration, usually diagnosed in early childhood, may lead to a mistaken impression that pulmonary sequestration is exclusively a pediatric concern. The case reported here illustrates that careful clinical and roentgenographic follow-up of nonresolving pneumonia in an otherwise healthy young adult may lead to the diagnosis.

Report of a Case

A 17-year-old woman, a college student and swimming instructor, presented to the emergency room at the University of California, San Francisco, with a two-day history of fever, cough and pleuritic chest pain. No chills were reported. Findings on physical examination were unremarkable except for mild tachypnea (respiratory rate 35), fever (39.6°C, 103.3°F) and decreased breath sounds over the left base. A roentgenogram showed a left lower lobar infiltrate and pleural effusion. Laboratory test results included a leukocyte count of 20,000 with a shift to the left, a blood culture which yielded no growth and a negative tuberculin skin test. The patient was given a single injection of intramuscular penicillin and discharged home on a regimen of oral penicillin.

At home, she improved and was asymptomatic and afebrile when reexamined five days later, except for persistent rales over the left base. A roentgenogram showed resolution of the pleural effusion but persistence of the left lower lobe infiltrate. Localized prominent rales also persisted in the area of the left posterior basal segment.

Three months later the patient continued to feel well when ambulatory but experienced paroxysmal coughing when recumbent. A small amount of thick, yellow sputum yielded no growth on culture and no organisms were detected on Gram stain and acid fast microscopic examinations.

Skin tests for tuberculosis, histoplasmosis, and coccidioidomycosis and coccidioidin titers were negative. Fine rales were still heard over the left base, and roentgenograms showed the persistent left lower lobe infiltrates (Figure 1). Bronchopulmonary cultures were again negative. The patient received postural drainage, chest percussion and pulmonary therapy for one month as an outpatient; there was no change in the findings and a pulmonary sequestration was suspected.

The patient was then admitted for elective bronchoscopy and bronchography. Bronchoscopy showed a noncommunicating density in the left lower lobe. Bronchography showed displacement of small airways, suggesting a mass lesion in the posterior basal segment of the left lung. The bronchial tree was not connected to the presumed mass. Aortography showed a left posterior basal segment sequestration supplied by two vessels from the aorta (Figure 2). Venous drainage was supplied by both azygous and hemiazygous systems. Left thoracotomy was carried out and a consolidated noncommunicating mass, consistent with a sequestration, was discovered lying within the left posterior basal segment, measuring approximately 14 by 14 by 12 cm. Two very thin-walled, tortuous vessels were identified directly connecting the aorta and the mass. A large venous tributary was also found. Gross examination showed a single, fresh tissue fragment. The specimen was firm with numerous small cystic spaces containing copious amounts of yellow-green purulent material. At one end several vessels were noted amidst a cluster of lymph nodes. Microscopic examination of the surgical specimen showed acute and chronic inflammation. The

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Dr. Crain's research supported in part by the Robert Wood Johnson Foundation.

Submitted, revised, May 17, 1978.

Reprint requests to: Lucy S. Crain, MD, Associate Director, Family/Primary Care Clinic, Div. of Ambulatory and Community Medicine, University of California, San Francisco, San Francisco, CA 94143.

postoperative course was complicated by a small bronchopleural fistula and consequent pneumothorax. Repair of the fistula required repeat thoracotomy several days after the initial operation. The patient's subsequent recovery was uncomplicated and roentgenograms showed no further infiltrate. Ten months following discharge, she continues to be asymptomatic.

Discussion

Pulmonary sequestration is a congenital malformation in which a portion of nonfunctioning lung is partially or completely separated from the normal tracheobronchial tree and receives its blood supply from aberrant vessels. An intralobar sequestration occurs within the visceral pleura of the normal lung, usually in the posterior basal segment—more often within the left than the right lung. Its systemic blood supply is usually from the abdominal or thoracic aorta.[1-3] An extralobar sequestration has its own pleural investment, is clearly separate from the rest of the lung and is almost always found on the left side. Its blood supply is also usually from anomalous systemic vessels.[1,2,4]

The system of venous drainage of pulmonary sequestrations is inconsistent. It is frequently reported that venous drainage of intralobar sequestrations is by way of the pulmonary veins, while venous drainage of extralobar sequestrations is by way of the azygous, hemiazygous or portal systems. Carter cited 11 cases involving the azygous-hemiazygous system, of which eight were intralobar and three extralobar sequestrations.[1] Our case also shows intralobar sequestration with hemiazygous and azygous drainage.

Pulmonary sequestration, although an unusual occurrence, is not rare. Ranniger and Valvasorri, in 1964, noted more than 250 reported cases.[5] Carter[1] reviewed 233 cases in 1969, and reported sequestration cysts in 1.1 percent to 1.8 percent of all pulmonary resections; 198 were intralobar, with a male to female preponderance of 1.5 to 1. Extralobar sequestrations showed a 3 to 1 male to female preponderance. Though most of these cases presented by the age of 7 years, the reported age at diagnosis varied from infancy through the eighth decade. DeParedes and co-workers[2] in 1975 reviewed 80 cases of infants and children; 56 were intralobar. They stated that the diagnosis of intralobar sequestration is rarely made in infancy, and more than 50 percent of patients with this diagnosis are over 20 years of age.

The origin of pulmonary sequestration is controversial. Pryce proposed a "vascular traction" theory, suggesting that the abnormality results from "traction between the sequestered mass anchored down by the abnormal blood supply,

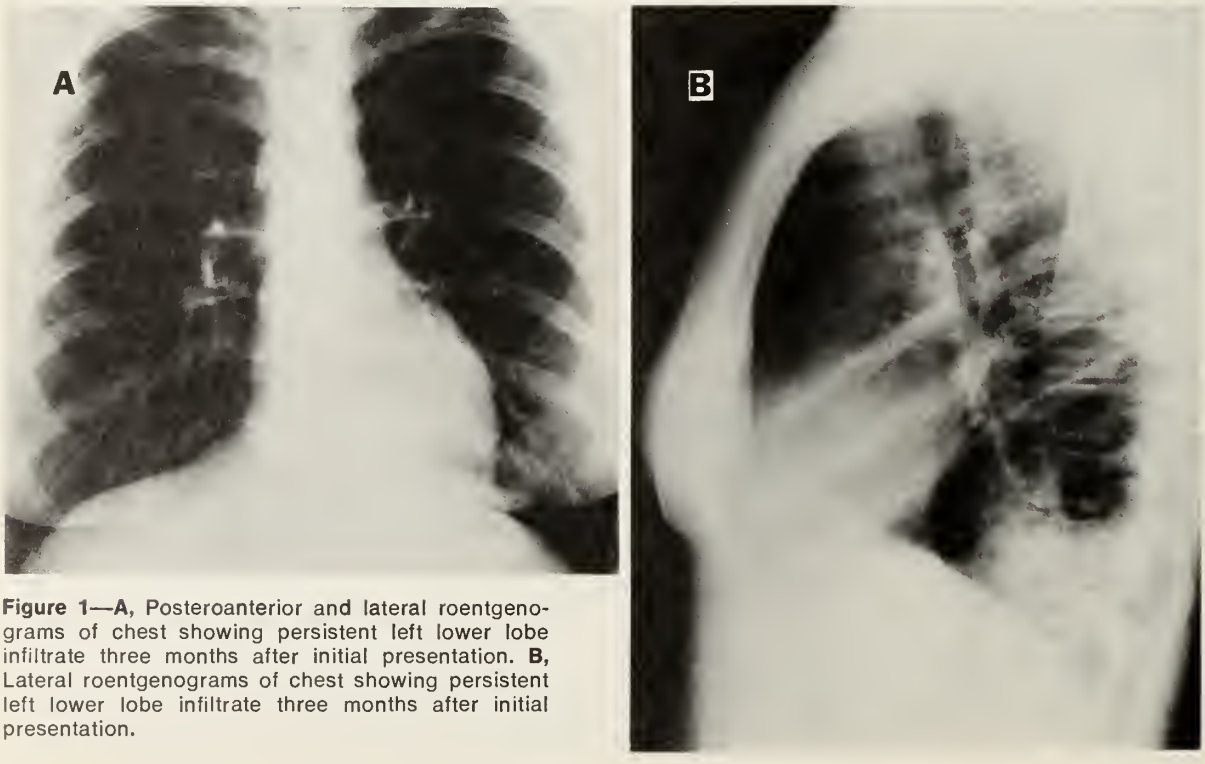

Figure 1—A, Posteroanterior and lateral roentgenograms of chest showing persistent left lower lobe infiltrate three months after initial presentation. **B,** Lateral roentgenograms of chest showing persistent left lower lobe infiltrate three months after initial presentation.

Figure 2.—Aortogram showing two arteries supplying a left posterior basal segment sequestration.

and the normal lung" during the embryological period, resulting in sequestration and secondary cystic degeneration.[8] Smith[4] rejected this theory and suggested that "the primary lesion in intralobar sequestration is some failure of the pulmonary artery in fetal life to supply the segment of lung involved," with persistence of systemic blood pressure leading to cystic and fibrous degeneration. Boyden,[9] based on then current embryologic data, postulated that there was "coincidental occurrence of lung cysts and systemic pulmonary arteries." He later suggested that a "lower accessory lobe" (extrapulmonary sequestration) may arise embryologically from an esophageal diverticulum.[10] A number of other authors have described the coexistence of abnormalities previously considered to be of separate origin.[6,7] From these cases have evolved the unifying etiological concepts about various pulmonary and bronchopulmonary-foregut malformations.[6-10]

Pulmonary sequestration may present in a number of ways, but the most frequent manifestations are respiratory symptoms with recurrent pneumonia,[1-3,16-18] although fever, hemoptysis, chest pain, respiratory difficulty with or without cyanosis, weakness, vomiting or feeding difficulty (particularly with extralobar sequestration in infants and children), anemia, cardiovascular problems (including congestive heart failure), lung abscess, atelectasis and bronchiectasis, have also been reported. The case presented suggests a paradox between the production of sputum presumably deriving from the infected sequestrum and the typical absence of communication between such a segment and the normal bronchial tree. The paradox might be explained by reestablished communication due to infection and erosion,[1] or by microscopic communications with the adjacent normal lung, allowing air and bacteria to enter the cysts of the sequesterial lung.[2] In asymptomatic patients, the diagnosis of a pulmonary infiltrate is frequently detected by incidental roentgenography.[1-3,16,17]

A sequestered portion of lung may be mistaken for a number of other conditions, including pneumonia, emphysema, bronchiectasis, lung abscess, tumor, bronchogenic cyst or an intrathoracic kidney.[1,19]

The diagnosis of pulmonary sequestration may be suspected from findings on a roentgenogram of the chest which initially may be indistinguishable from pneumonia. However, after treatment with antibiotics the radiographically shown area of density remains.[1,2,10,19] Tomography occasionally suggests the presence of an abnormal blood supply.[18,21] Bronchography usually shows displacement of adjacent normal small airways by the space-occupying lesion; contrast material in cystic areas is an inconstant finding.[5,22,23] Arteriography, which can establish the definitive diagnosis of this condition and preoperatively define the blood supply, shows the aberrant vessel or vessels usually arising from the thoracic or abdominal aorta and entering the sequestered segment.[1,2,18,24-27]

A technical operative risk is the accidental transection of a systemic vessel which then retracts below the diaphragm with resulting uncontrollable hemorrhage.[14,30,31] Treatment of symptomatic pulmonary sequestration is by surgical excision (either segmental resection or lobectomy).[28,29]

Summary

Nonresolution of radiographic and auscultatory evidence of pneumonia in a 17-year-old woman led to additional diagnostic considerations. The definitive diagnosis of intralobar pulmonary sequestration was established by arteriography. A review of the literature suggests that this entity should be recognized by primary physicians as an infrequent cause of recurrent pneumonias in patients of any age.

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Bleeding From Aspirin Prophylaxis of Coronary Disease

I RUN A LABORATORY in which we see a lot of bleeding complications and we are beginning to diagnose a new syndrome, at least in Boston, which occurs in persons taking aspirin to prevent coronary disease, who are presenting with increasing frequency with gastritis, hemorrhagic gastritis or generalized bleeding. We are impressed with the frequency with which people who take aspirin have bleeding. I think that until hard data are in, one should not assume that the ingestion of aspirin, even in small amounts, is a benign thing to do. At least in a subset of people I am impressed that it can precipitate or unmask hemorrhagic diathesis.

—DANIEL DEYKIN, MD., *Boston*

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Dietary Fiber

TO THE EDITOR: Dr. David Kritchevsky cites in his article "Metabolic Effects of Dietary Fiber" in the February issue (West J Med 130:123-127, Feb 1979) the work of Watanabe and co-workers[1] who tested several dietary fibers for their effect on the appearance of chemically induced colon tumors in rats. Similarly, Cruse and associates,[2] using injection of dimethylhydrazine (DMH) to induce colon cancer, recently failed to demonstrate a protective effect of dietary fiber (bran).

The problem is that this kind of experimental approach is unsuitable to test the fiber/bran hypothesis. It has not been shown that parenteral DMH or one of its metabolic products (given they are carcinogenic) causes neoplastic changes from the *luminal side* of the colonic mucosa. According to Burkitt[3] and others the addition of fiber to the diet (for example, in the form of bran)

- decreases the intestinal transit-time of the feces (the reproducibility and importance of this finding is still debated),
- increases persistalsis and fecal bulk, thus diluting potential carcinogens and decreasing their contact time with the bowel mucosa,
- possibly affects the composition of the intestinal flora
- and inhibits the bacterial degradation of bile acids and possibly other, potentially carcinogenic, fecal constituents.

Hence, on the basis of these suggested mechanisms one cannot expect that fiber exhibits any protection against colonic tumors that are induced by *injection* rather than *ingestion* of carcinogens such as DMH. Even if such an approach yields a protective effect[4] it must be regarded as irrelevant. The same arguments apply to the, similarly unphysiologic, intrarectal instillation of azoxymethane.

Kritchevsky's suggestion that the effect of fiber in experimental colon carcinogenesis depends on the type of fiber and the *mode of administration* of the carcinogen is supported by studies that use a physiologic approach to simulate the probable environmental origin of human colon cancer.[5,6] These experimental investigations suggest that fiber (bran) may in fact be protective.

As of now there is no scientific *proof* of the prophylactic effect of bran. However, disease prevention does not necessarily require a complete understanding of the biological mechanisms involved before some action is undertaken. Since the ill effects of bran are nil (apart from some increased flatulence in the initial stages), the effect on bowel habits is beneficial. Moreover, bran is cheap; it might well be worthwhile and feasible to change our diets by daily addition of bran. Or as Burkitt has put it: "Heads I win and tails I don't lose."

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School of Public Health
University of California, Berkeley

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* * *

Dr. Kritchevsky Replies

TO THE EDITOR: I am in complete agreement with Dr. Kochen's views on the experimental approach to investigations of dietary effects on colon carcinogenesis. As he notes, I suggested in my article in the February issue that data obtained from experiments in which the putative carcinogen was administered orally were the most meaningful. Fiber may have local effects on bowel mucosa[1]

which will act to enhance the carcinogenic effects of rectally instilled agents.

While I am not impressed by the "it can't hurt" school of medication, bran may be helpful in certain instances.

DAVID KRITCHEVSKY, PhD
Wistar Institute of Anatomy and Biology, Philadelphia

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A Pediatrician's Advice to Patients

To THE EDITOR: Below is a letter that I have recently distributed to my patients. It seems to me that it may be of interest to other readers of the WESTERN JOURNAL.

To My Patients:

Your questions and the current publicity associated with Family Centered Childbirth Programs and Alternative Delivery Methods prompts this letter to express my concern regarding the adequacy of the medical supervision that is provided newborn infants when one of the new and different childbirth programs is chosen by parents.

Although the vast majority of deliveries occur without *any* difficulties, for either mother or infant, we should be reminded that immediately after birth, a number of vital changes begin taking place within the infant's body. During this time, the baby's survival and the prevention of brain damage depends upon the rapid and successful completion of these changes. It is therefore wise to be extremely cautious during the first hour or so of each newborn infant's life in order to help avoid any delay in detecting the occasional infant who is developing unsuspected problems.

The newborn care information given to parents during prenatal courses is incorrect if it portrays the newly born infant as a cute little toy to be loved and played with a few short minutes after birth, without pointing out the risks to the newborn during the first hour or so of its life.

Because the welfare of newborn infants is perhaps the most important topic in the whole field of pediatrics, I would like to share with you a summary of my recommendations:

A. The focus of attention during the first 30 to 60 minutes of life should be directed to the close supervision of and support for the baby's breathing and oxygen needs, heart and circulation, central nervous system, blood sugar and temperature stability. To initiate a program of skin-to-skin contact, breast nippling and infant-parent cuddling in the birth room or mother's recovery room *before* the baby has passed through a 30- to 60-minute recovery period can *increase* the risks for the baby.

B. Breast nippling, skin contact and cuddling with the parents *prior* to a 30-minute infant recovery period provides no short- or long-term benefits to the mother or infant that are not provided *equally well* by these same activities *after* the baby's successful recovery period.

Should you be expecting a new baby and intend having me as the pediatrician, please advise hospital labor and delivery room staff that my recommendations are these:

1. Upon delivery and after a satisfactory Apgar score, the baby quickly "says hello" to parents in the delivery or birth room, and then is immediately transferred to the radiant heater in the newborn infant recovery facility (Newborn Nursery in most hospitals).
2. Newborn Nursery nurse to call me promptly regardless of the hour, reporting the baby's birth and nursery admission status and arrange care during the recovery period.
3. After a 30- to 60-minute recovery period, if stable behavior has been identified, the baby may visit parents freely and initiate continuing rooming-in, etc., per their wishes, under the supervision of the Newborn Nursery staff.
4. Parents are encouraged to phone me should they have any questions after the infant's birth.

Please do not hesitate to call if you have questions or suggestions regarding these recommendations.

ROBERT F. L. POLLEY, MD
Seattle

Of Cults and Armageddon

To THE EDITOR: This is in response to the editorial "Of Cults and Armageddon" in the January 1979 issue.

I am troubled by your use of the holocaust in Nazi Germany against the Jewish people in juxtaposition with the events in the Jim Jones settlement in Guyana last year.

After personally visiting Auschwitz, Poland, in October 1976, I cannot accept your conclusion that "they [the German people] were somehow swept along by a charismatic and irrational leader. . . ." The scope of the death camps, the careful research and development in murder, and the energies and materials expended to reach a "final solution" of the Jewish question makes me reach another conclusion. To wit, the Polish-German people supported these actions coolly and with malice. Hitler's only mistake was not winning. I do not know when Armageddon will come but I do not think the scenario is simply explained by "normal people" following a leader without thought.

MICHAEL J. FRANZBLAU, MD
San Rafael, California

OHS Syndrome

To THE EDITOR: In their article "The Obesity-Hypoventilation Syndrome" in the November 1978 issue, Morgan and Zwillich noted that several designations, including Pickwickian syndrome, have been used for the illness they discuss. They prefer, however, the name obesity-hypoven-

tilation syndroms (OHS), "which emphasizes the abnormal ventilation found in these patients."

I would suggest a slight modification in the suggested name change in order to emphasize all three parts of the triad. My suggestion is *obesity, hypoventilation and somnolence syndrome* (OHS *syndrome).*

Abbreviations are becoming a first-class problem in every field. In medicine, different interpretations are placed on the same abbreviation depending on the field of medicine or science the listener relates to. According to *The Doctor's Shorthand* by Cole,[1] OHS is unclaimed. Curiously I can find no abbreviation for syndrome. To me it would seem best if all three parts of the triad were in the abbreviation and the word *syndrome* followed it so that future generations of physicians would have a clue as to what the initials stood for.

ROBERT HAWKINS, MD
Santa Barbara, California

REFERENCE

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Community Hospital Continuing Medical Education

TO THE EDITOR: Alvin Lee Block's letter "Community Hospital Continuing Medical Education—A Missed Opportunity" in the January issue correctly emphasizes the benefits of programing most educational activities at community hospitals. More and more hospitals in California are now accredited by California Medical Association (CMA) surveyors to plan and produce educational programs. The quality and relevance of these programs varies widely and in fact cannot really be monitored by the CMA.

Several reasons for ineffective programs can be mentioned: (1) Few doctors in community hospitals have experience or training in planning problem-oriented educational programs, the usual recourse being to get an "interesting speaker," preferably on a topic of general interest. (2) Although recommended by CMA, the design of educational programs is therefore often not based on patient care problems. As a result, (3) the visiting expert may not focus his lecture on what the audience needs and wants to hear.

To deal with these points, this medical school has developed a system which provides professional educators (not physicians) to serve community hospitals as itinerant directors of medical education. They meet with hospital education committees to plan programs tailored to the needs of the medical staff, and the medical school provides appropriate faculty experts who plan their lectures and discussions to address the specific educational objectives. In all cases attempts are made to derive these objectives from demonstrated or clearly felt problems of local doctors.

This system seems to work in a large metropolitan area, and adaptations may be needed for areas not close to a medical school. Nevertheless, with some imagination and interest in encouraging the development of community hospitals as the major sites for physicians' continuing medical education, similar systems can be developed that can serve the needs of most doctors.

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Trauma Rounds

Chief Discussants
CHRISTOPHER C. BAKER, MD
DAVID C. HOHN, MD

Editors
DONALD D. TRUNKEY, MD
F. WILLIAM BLAISDELL, MD

This is one of a series of Conferences on Trauma at San Francisco General Hospital

Refer to: Baker CC, Hohn DC: Sepsis in trauma patients (Trauma Rounds—San Francisco General Hospital). West J Med 130:378-383, Apr 1979

Sepsis in Trauma Patients

DONALD D. TRUNKEY, MD:* In this Trauma Rounds we will depart from our regular format of patient presentation. Instead, we will examine the problem of sepsis in surgical patients, and also discuss the improved treatment and prevention of septic complications. During the past five years at the Trauma Center, sepsis (and its sequelae) has become the leading nonneurologic cause of morbidity and mortality in the postoperative state. Last year sepsis alone accounted for more deaths than did cardiogenic shock and hypovolemic shock combined.

Figure 1 shows the major interactions that influence the development of a septic focus after injury. Although clinicians cannot control the situational factors of the inoculum, the virulence or the tissue damage, they can substantially modify the host resistance and iatrogenic factors that also contribute greatly to the development of sepsis. There are additional iatrogenic and systemic causes of decreased resistance not listed in the figure but which include patient age and antecedent diseases such as diabetes. Table 1 lists local wound factors that can interfere with host resistance and also contribute to the development of a septic focus. With this introduction, let us examine more closely some of the components making up this triangle of interactions. To begin, Dr. Christopher Baker will discuss host resistance.

CHRISTOPHER C. BAKER, MD:† As Dr. Trunkey has just pointed out, sepsis is now the major cause of death in patients who have suffered burns and trauma. Along with the progressive development of more sophisticated antibiotics, we have also seen the emergence of exotic, highly resistant pathogens which were thought previously to be nonpathogenic bacteria and fungi. Since the mortality from sepsis has not changed significantly during the past 30 years,[1] we believe it is crucial to focus our attention on the principles of host resistance and immune defenses in order to find some possible solutions to this new set of problems.

Host Resistance and Phagocytosis

The major aspects of host resistance are shown in Table 2. These factors are critical throughout the four major steps in the phagocytic process: chemotaxis, opsonization, ingestion and killing.[2]

Chemotaxis can be effected by substances released by bacteria, but a more important pathway is via the complement cascade. The $\overline{C142}$ complex cleaves C3 and C5 to produce C3a and C5a, with C5a being the major chemotactic factor.[2] Chemotaxis is also promoted by clotting (kallikrein and plasminogen) and lymphokines. Op-

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sonins (from the Greek *opsono*, "prepare food for") are substances that render bacteria more susceptible to ingestion by phagocytes. Opsonization can be accomplished by a specific natural antibody to the bacterial capsule (for example, pneumococcus), by an antibody plus complement (which activates C3 to C3b), or by the heat labile alternate properdin pathway.[3]

During the process of ingestion the phagocyte forms pseudopods, which surround the microbe to form a phagosome. Leukocyte granules are specialized lysosomes which contain such lethal agents as myeloperoxidase and lactoferrin; the granules fuse with the phagosomes, releasing their enzymes to kill and digest the bacteria. Tables 3 and 4 show factors that depress neutrophil function and the reticuloendothelial system, and these factors should be kept in mind when caring for patients who are at risk for sepsis.

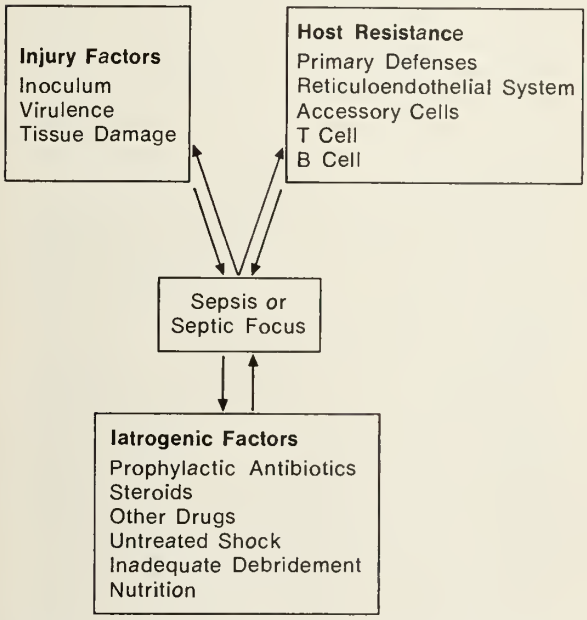

Figure 1.—Major interactions that influence the development of a septic focus after injury.

TABLE 1.—*Local Wound Factors That Interfere With Host Resistance*

Necrotic tissue
Decreased wound perfusion
Foreign body
Sutures
Hematoma
Dead space

TABLE 2.—*Major Factors in Host Resistance*

Humoral:	
Immunoglobulin	Chemotaxis
Complement	Opsonization
Properdin	Bacteriolysis
Cellular:	
Polymorphonuclear leukocytes	Phagocytosis and killing of microorganisms
Mononuclear leukocytes & macrophages	
Eosinophilic leukocytes	

TABLE 3.—*Factors Depressing Neutrophil Function*

Alcoholic hepatitis	Intracellular alkalosis
Burns	Major trauma
Congenital disorders	Malignancy
Diabetes mellitus	Renal transplantation
Disseminated intravascular coagulation	Shock
	Steroids
Hematoma/scroma	Vasoconstrictors
Hypophosphatemia	White cell antigens
Hypoxia	

TABLE 4.—*Factors Depressing the Reticuloendothelial System*

Autoimmune diseases	Sarcoidosis
Dextran	Sickle cell disease
Enhancing antibody	Splenectomy
Fibrin debris	Starvation
Intracellular parasites	Steroids
Irradiation	Stroma-free hemoglobin
Lymphoma	Transfusion reactions
Prostaglandins	

Immunologic Considerations

The three types of immunocompetent cells are thymus-derived (T) cells, bone marrow-derived (B) cells and accessory (A) cells, or macrophages. The human immune system is very tightly regulated and stimulatory and inhibitory cells interrelate in numerous complex fashions. We hypothesize that insults such as burns or trauma upset this delicate balance, giving rise to a predominance of T suppressor cells or inhibitory A cells (or both), which subsequently leads to the immune depression that has been shown to exist in such patients.

To illustrate our hypothesis, let me present some of the data that we have accumulated in our patient studies. Trauma patients in whom splenectomy was done were shown to have a pronounced depression of the response of their lymphocytes to the T cell mitogen, phytohemagglutinin, which was maximal 13 to 16 days after operation, but which returned to normal levels within 30 days after injury.[4] This depression was significantly lower than the response level not only of normal control patients but also of trauma

TABLE 5.—*Therapeutic Considerations*

Carry out delayed primary closure of contaminated wounds.
Drain abscesses/hematomas.
Maintain tissue perfusion and oxygenation.
Avoid use of steroids, vasoconstrictors, diuretics, dextran.
Maximize nutritional support.
Treat coagulopathies aggressively.
Treat with fresh frozen plasma, bacterial immunization, hyperimmune globulin, immunotherapy.

patients not having had splenectomy. Concomitantly, the leukocytes of trauma patients who have had splenectomy were shown to be capable of suppressing an ongoing, normal, one-way mixed lymphocyte reaction.[5]

Furthermore, recent data from our laboratory seem to indicate that these effects are due to the presence of an inhibitory macrophage.[4,6] If confirmed, these observations would correlate well with the hypothesis that removal of the spleen, which is a major portion of the reticuloendothelial system, causes impaired clearance of inhibitory macrophages from the circulation.

Our studies of burn patients have shown a depression in the phytohemagglutinin response occurring five to ten days after injury.[7] We have subsequently been able to recognize several patterns of phytohemagglutinin response, which, when correlated with the clinical course, allowed us to predict accurately the development of severe sepsis. As in splenectomy patients, in burn patients leukocytes were also found to be capable of suppressing a normal mixed lymphocyte reaction, and further experiments suggest that this defect is due to a suppressor T cell.[6] Although animal data have shown no defect in B cells after burns,[8] nutritionally-deprived animals seem to have major defects in B cells and antibody production.[9]

A number of therapeutic considerations which naturally arise from this discussion are shown in Table 5; the last category lists certain alternatives which are under investigation but are at present somewhat tentative. Alexander has shown restoration of depressed serum opsonin levels after administration of fresh frozen plasma,[10] and he suggests that the incidence and the mortality of burn sepsis may be lowered by use of pseudomonas vaccine and hyperimmune globulin.[1] Because prostaglandins have also been shown to inhibit macrophage function,[11] it may be that patients with A-cell defects will be treated in the future with prostaglandin inhibitors such as indomethacin or aspirin or with A-cell stimulants such as Bacillus Calmette-Guérin vaccine (BCG). Further immunologic research will no doubt provide solutions to many of these problems encountered in caring for patients with sepsis.

DR. TRUNKEY: We will now examine the third component contributing to the development of sepsis. Dr. David Hohn will discuss the iatrogenic factors.

DAVID C. HOHN, MD:* Now that Dr. Baker has outlined for you the normal mechanisms of resistance in the unimpaired host, I would like to review several iatrogenic factors that can impair natural resistance to sepsis. Among these factors are the use of certain classes of drugs, malnutrition and tissue hypoxia (Figure 1). As already noted, the process whereby an invading microorganism is contained involves a complex series of integrated humoral and cellular functions. Inhibition of any one of these functions can produce a crack, and perhaps only a very small crack, in the armor of host defense.[12]

Antibiotics

We all, on occasion, attempt to augment host resistance by administration of broad spectrum antibiotics. Accumulating evidence, however, suggests ever more strongly that the misuse of antibiotics is the single greatest iatrogenic factor in the production and perpetuation of sepsis.

First, antibiotics are, by definition, microbial poisons and on occasion may be toxic to the host as well as to the microbe. A recent review of antibiotic side effects showed that in 4,000 antibiotic administrations an identifiable adverse response developed in some 5 percent of patients. About 50 percent of these reactions were significant enough to delay discharge of patients from the hospital, and 10 percent of reactions were severe.[13] It is sobering to recall nearly 100 deaths per year in the United States result from anaphylaxis due to penicillin administration. In addition, there are untold numbers of patients with clinical or subclinical nephrotoxicity and ototoxicity secondary to aminoglycoside usage as well as rare cases of marrow aplasia and overwhelming membranous colitis from chloramphenicol and clindamycin, respectively.

In addition to such obvious toxic side effects, antibiotics may also cause more subtle disturb-

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TABLE 6.—*Guidelines for Microbial Diagnosis and Surveillance*

Monitor local microbial ecology for detection of
Nosocomial outbreaks,
Changing antibiotic sensitivity patterns,
Wound infection rates.
Minimize blind use of antibiotics by appropriate culture and sensitivity determinations.
Culture for anaerobes.
Be suspicious of "nonpathogens," especially in immunodeficient patients.
Consider exploratory operations for diagnosis and microbial isolation in selected cases.
Use sonograms, gallium scans or computed tomographic scans to localize clinically inapparent abscesses.

TABLE 7.—*Therapeutic Guidelines for Antibiotic Usage*

Never rely on antibiotics when incision and drainage are indicated.
Therapeutic antibiotic usage:
Use an appropriate antibiotic in an adequately high dosage,
Repeat cultures—the flora may change,
Terminate antibiotics as soon as is safe.
Prophylactic antibiotic usage:
Use only when benefit/risk ratio is high,
Use drug for anticipated flora in high concentrations,
Administer preoperatively,
Discontinue promptly—within 24 to 48 hours.

ances of host defense mechanisms. Alexander has recently shown that several antibiotics may greatly impair neutrophil chemotaxis *in vitro*.[14] Tetracycline, erythromycin, nafcillin and sulfadiazine were shown to be active in this regard, while chloramphenicol actually augmented chemotactic function. The other commonly used antibiotics had little or no demonstrable effect. Similarly, Warden and his colleagues showed that sera from burn patients being treated with topical sulfadiazine inhibited chemotaxis by normal neutrophils.[15] The inhibiting substance was shown to be sulfadiazine, which was absorbed through the burn wound. No one would debate the use of sulfadiazine in selected patients with burn wound sepsis, but we may pay a price in host resistance for the benefits derived.

Proteolytic cleavage of complement factor 3 is required for optimal generation of opsonic factors. Alexander has shown that under certain circumstances, C3 cleavage can be inhibited by pharmacologic concentrations of tetracycline, sulfadiazine or gentamycin. While the clinical significance is unclear, the implications of such findings are evident.

Work with genetic disorders of phagocytosis has amply proved the critical importance of phagocytic function in host defense. In this regard, Lehrer has shown that physiologic concentrations of chloramphenicol caused blockage of postphagocytic metabolic activation in neutrophils.[16] This group has also shown that incubation of phagocytes with sulfa drugs may impair intracellular killing of certain fungi. Again, the clinical significance is unknown but the findings provoke concern.

Antibiotics such as rifampin and chloramphenicol function by inhibition of nucleic acid synthesis. Experimentally, high doses of these drugs have been shown to inhibit synthesis of IgG and to impair T-cell function.

Perhaps the most serious side effects of antibiotics are not those manifested in the host but rather the effect of antibiotics on the nosocomial environment. As late as 1960, organisms such as Pseudomonas and Serratia were considered nonpathogens, but we are all aware of the potentially devastating pathogenicity of these organisms and of the overwhelming problem posed by the emergence of resistant strains as a consequence of antibiotic usage. If the guidelines listed in Tables 6 and 7 are followed when selecting and using antibiotics, the problems of toxicity and adverse nosocomial effects can be kept to a minimum.

Corticosteroids

With the exception of cytotoxic chemotherapeutic agents, no drugs have a more deleterious influence on host resistance mechanisms than do the corticosteroids. With the burgeoning interest in the use of high dose steroids in *treating* sepsis, it is pertinent to review the various deleterious side effects of steroids.

One of the most easily shown adverse effects of steroids is the inhibition of chemotaxis, and this effect has been found with cells *in vitro* as well as *in vivo* by the use of Rebuck skin window techniques. Polymorphonuclear leukocytes are the cells most inhibited by steroids, although the influx of mononuclear inflammatory cells is also delayed. In addition, the febrile response to infection is blunted by steroids, making the recognition of sepsis more difficult. Steroids do not appear to hamper ingestion and killing of most organisms by neutrophils, but recent studies indicate that steroids suppress the killing of certain bacteria and fungi by monocytic cells.[17]

Clinically, perhaps the most familiar influence of steroids is the pronounced inhibition of cell-

mediated immunity (T lymphocyte function). Loss of previously present delayed hypersensitivity response (anergy) may occur, with exacerbation of tuberculosis, development of unusual viral or fungal infections or even parasitic infestations. Steroid-induced tolerance to allografts is also indicative of profound inhibition of cell-mediated immunity.

Synthesis of immune globulin by B lymphocytes and plasma cells is relatively resistant to the effect of steroids. Clinically significant reduction of serum immune globulin has been shown only with very high dosage schedules.

The major clinical significance of these effects of steroids has been shown in numerous animal experiments, in the practice of immunosuppression for organ transplantation and in clinical studies in patients receiving chronic steroid therapy. All of these studies lead to the same conclusion: corticosteroid therapy causes increased susceptibility to infection, particularly when high dosage schedules are used for prolonged periods.

When steroids must be used, three recent observations should be borne in mind. First, some of the synthetic steroids, such as dexamethasone, do not impair neutrophil mobilization and may even enhance mobilization. Second, as has been shown by Dale and colleagues,[18] use of alternate day schedules for steroid administration is associated with a significantly lower incidence of infectious complications—presumably due to recovery of immune function during the day without therapy. Last, administration of vitamin A can partially block the deleterious effects of steroids on tissue repair.

Other Drugs

In addition to antibiotics and corticosteroids, several other drugs produce experimentally detectable alterations in host defenses.

Of the antiinflammatory agents, colchicine exerts its biologic effect in gout by blocking phagocytic uptake of urate crystals. Similarly, colchicine-treated leukocytes show impaired uptake of other types of particles as well as impaired postphagocytic release of lysosomal enzymes. Phenylbutazone stabilizes lysosomal membranes and may impair release of digestive enzymes into the phagocytic vacuole. Even aspirin may have a deleterious effect by reducing the adhesiveness of phagocytes; this has also been shown to occur following ethanol ingestion. Incubation of leukocytes in the presence of ascorbic acid has caused reduced fungicidal activity. While none of these drugs alone causes clinically significant susceptibility to infection, cumulatively they may contribute to the impaired resistance of the compromised host. Finally, through their cytotoxic actions chemotherapeutic agents undoubtedly predispose patients to infection.

Malnutrition and Host Defense

There is little question that severe malnutrition predisposes to infection. This conclusion is derived from both clinical studies of subjects with kwashiorkor and animal starvation studies. Results from clinical studies of surgical patients also suggest a correlation between septic complications and malnutrition, and a number of abnormalities in host defense mechanisms occur in severe malnutrition.[19]

Histopathologic changes in severe protein calorie malnutrition are especially evident in thymic tissue, lymph nodes and the spleen. Thymic weight is decreased, as is cellularity; the number of the Hassall corpuscles is diminished, and there is distortion of cellular architecture. Lymph nodes and spleen are depleted of lymphocytes in paracortical and paraarteriolar areas respectively, and the numbers of primary follicles and germinal centers are similarly reduced.

Alterations in T lymphocyte cell mediated immunity with malnutrition include lymphopenia, diminished mitogenic response to phytohemagglutinin and decreased T rosette formation. Impaired skin test response to standard antigens has been shown *in vivo,* as well.

Altered B lymphocyte and plasma cell function in protein calorie malnutrition has been more difficult to show, and there have been some conflicting findings. Since immune globulins and complement factors are proteins, one might anticipate that these factors would be deficient when protein synthesis is nutritionally impaired. Abnormally low immunoglobulin titers have been found in animal experiments, but high titers are present in children with kwashiorkor. Primary specific antibody production may be blunted or even augmented, depending on the antigen employed, and the anamnestic response following second challenge with an antigen is usually fully preserved. Serum levels of complement factors may be subnormal. This is particularly true for C3, an observation that may in part explain the impaired bacterial opsonization and chemotaxis of phagocytes in malnutrition. Phagocytic uptake of bac-

teria and fungi appears to be well preserved in malnutrition, but the kinetics of cellular killing of ingested microbes may be slow. While none of these individual deficiencies is likely to be of great clinical importance, the combined immune deficency state seen in severe malnutrition may cause profound predisposition to infection. It has been stated that "the best prophylactic antibiotic is adequate nutrition." Certainly nutrition is the safest prophylactic antibiotic as well.

Tissue Hypoxia

Another iatrogenic factor in sepsis is tissue hypoxia, a subject that we have studied rather extensively in our laboratory. It is now abundantly clear that one of the major intracellular killing mechanisms of phagocytes is dependent upon the presence of molecular oxygen. An active oxidative enzyme system in the phagocytic cell reduces oxygen to a number of highly toxic substances in the phagocytic vacuole and these oxygen-derived substances mediate the killing of the ingested microbes. Children in whom there is a genetic deficiency of this oxidative enzyme system are profoundly susceptible to clinical infection. We have postulated and shown that deprivation of oxygen causes an identical defect in phagocyte killing function.[20] It also appears that the levels of oxygen found in traumatic and infected wounds are sufficiently low to paralyze this important killing mechanism. In this regard the importance of maintaining circulatory and respiratory function cannot be overemphasized.

Sepsis

A final emerging concept is that sepsis itself causes major immunodeficiency, thereby creating a vicious self-propagating cycle that can lead inexorably to overwhelming sepsis and death. Immature neutrophils, or band forms, are less motile and may not kill bacteria as effectively as their mature counterparts. Alexander has recently provided evidence that sepsis may lead to depletion of critical opsonic proteins with the development of a consumptive opsoninopathy. Early work suggests that transfusion of fresh frozen plasma may, in part, restore opsonins and may also be of therapeutic benefit.[21]

In conclusion, it should be pointed out that although none of these iatrogenic factors alone is likely to be of great clinical importance, they often occur together in surgical patients and cause a very major crack in the armor of host defense.

DR. TRUNKEY: In summary, sepsis is now recognized to be the most common nonneurologic cause of postinjury morbidity and mortality. Although our ability to treat sepsis has improved in recent years, prevention will have a greater impact on survival. Today we have discussed some of the factors that may increase the risk of sepsis in trauma patients and how these factors may be moderated.

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The WAMI Program: A Progress Report

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IN THE LATE 1960's and continuing into the early 1970's, a series of innovations in medical education were initiated in the United States. These occurred concurrently with a massive increase in the number of applicants to medical schools[1] and a perception that this country was facing a health care delivery crisis.[2] Among these educational innovations were the development of organ system approaches to teaching,[3] independent study programs,[4] the use of computers in learning,[5] the development of family medicine departments in schools of medicine[6,7] and the initiation of decentralized medical education programs.[8,9] One of the latter efforts, the WAMI (an acronym for Washington, Alaska, Montana and Idaho) program was established in 1970 to meet the needs of the Pacific Northwest and Alaska. The preliminary outcomes of the WAMI program were encouraging and were reported in this journal in 1974.[10] The present report describes the developments in the WAMI program since then and shows that the goals of the program are being or have been achieved.

The WAMI Region

The states of Washington, Alaska, Montana and Idaho, the WAMI states, represent 22 percent of the land mass in the United States and contain approximately 6 million people. Two thirds of the physicians and other health professionals in this region live in three areas including the Puget Sound region of Washington, the Anchorage area of Alaska and the Treasure Valley of Idaho. The remaining third practice in the towns and rural communities of a region stretching across five time zones.

The University of Washington in Seattle has the only medical school in the WAMI region. Because much of the land is mountainous and inaccessible, the population is sparse and widely separated. In the past 15 years various local and regional attempts by state and federal agencies to find solutions to the health problems of this region have proved to be ineffective and at times counterproductive.

The Health Problems in the WAMI States

The WAMI program, which was proposed in 1970, was designed to meet four major health challenges in the Pacific Northwest and Alaska.

1. *Admission to Medical School*

Beginning in the late 1960's a progressively greater number of students applied for admission to medical school without a corresponding increase in the class sizes of medical schools. This increase was especially important for states without medical schools because state-supported schools have traditionally afforded their own residents preferential access to the positions available. Admissions of out-of-state students have been uncertain and in the face of increased resident applicants were expected to be curtailed.

2. *Lack of Primary Care Physicians*

In 1970, or the year the WAMI program was proposed, the WAMI states had too few family physicians, primary-care internists and primary-

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care pediatricians. This deficiency was especially severe in the more rural areas of the WAMI states.

3. *Maldistribution of Physicians*

In the early 1970's the majority of the physicians were located in the cities and larger towns, leaving large, sparsely populated areas with too few health professionals. When the geographic maldistribution was coupled with an insufficient number of primary care physicians, a severe shortage in the remote areas of the WAMI states was evident.

4. *Access to Education and Health Care Resources*

Physicians in isolated communities have restricted access to educational resources. Because of this, physicians have felt isolated and physician turnover has been significant.

In 1970 only a limited number of tertiary health care centers existed in the WAMI states. Since 18 major health care centers—including a neonatology center, a burn and trauma center, an epilepsy center, and a child development and mental retardation center—existed at the University of Washington Health Sciences Center and since there are no additional centers of these kinds in the region, it seemed desirable to find a way to bring these resources to communities with health care needs.

Finally, the WAMI states did not have the fiscal resources to build and maintain additional medical schools. It was recognized, therefore, that any program designed to meet the health care and health education needs of the region could not include capital expenditures for new facilities.

A Two-Phase Program

There are two separate phases in the WAMI program. In the first or *university phase,* four universities that do not have medical schools provide the first year of the medical school curriculum to medical students. This has allowed expansion of the entering class from 102 to 175, with 10, 20 and 20 first year position being reserved for Alaska, Montana and Idaho, respectively. In the 1977-78 academic year, 73 of the 175 students received their first year of training at Washington State University, the University of Alaska, Montana State University and the University of Idaho.

Courses for the university phase are planned conjointly by faculty from the five universities so

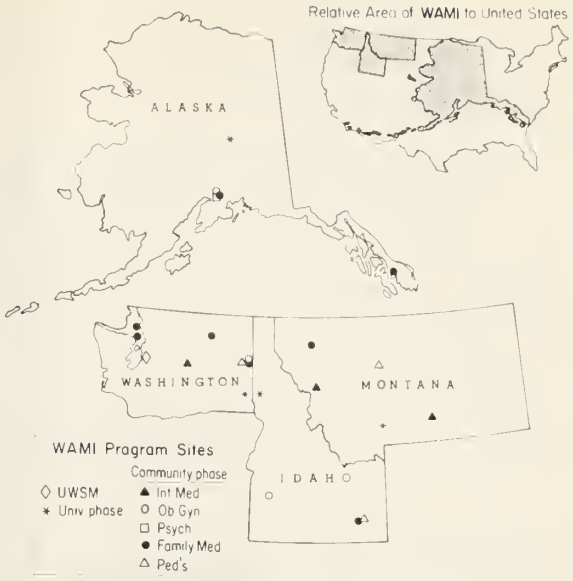

Figure 1.—WAMI program sites, 1979.
UWSM = University of Washington School of Medicine
Univ. Phase = university phase
Int. Med. = internal medicine
Ob. Gyn. = obstetrics and gynecology
Psych. = psychiatry
Family Med. = family medicine
Peds. = pediatrics

that a "single, region-wide course" is taught at five locations by a "region wide" faculty. Medical faculty from Seattle travel to the universities to cover those portions of the courses where more than local faculty resources are needed. To monitor the academic quality of the program and to determine whether students are learning in the required way, a continuous and extensive evaluation program is conducted.[11]

At the end of the first year all students go to the University of Washington campus in Seattle for the second year of the curriculum and for the initial clerkships in the third year of the undergraduate medical educational process.

Students then have the opportunity of participating in the second or *community phase* of the WAMI program. In this phase, students spend six weeks in community clinical units (CCU's) working with private physicians in rural communities in the four states. House staff officers in residency programs are also assigned to the CCU's for two to six months. These experiences in family medicine, internal medicine, pediatrics, psychiatry, and obstetrics and gynecology (Figure 1) are designed to provide a participant with an understanding of how the community is structured and functions, what roles a physician must play in such a community, and what skills and knowledge are required to deliver high-quality health services in

such a community. It was hoped that with such exposure, larger number of physicians would be attracted to careers in primary care in underserved areas.

At least once every six weeks medical faculty from the medical school in Seattle visit each unit. During these visits faculty members review the progress of the students and residents, act as consultants to the practicing physicians and provide formal continuing medical education to all health professionals in the area. In this way the educational and patient-care resources that exist in Seattle are made available to the faculty and patients of the community clinical units as well as to other health professionals who practice in the area.

Program Developments Since 1974

A number of major developments have occurred in the WAMI program since 1974.

- For the classes that entered in the fall of 1975, 1976, 1977 and 1978, 40 residents of Alaska, 79 residents of Idaho, 80 residents of Montana and 477 Washington residents were admitted to the University of Washington School of Medicine. This was achieved by establishing for each of the AMI states separate "interviewing" committees, which had as members University of Washington School of Medicine (UWSM) faculty and representatives from the individual states. A member of the UWSM faculty chaired each of the AMI interviewing committees.

- Since the advent of the program, 403 students have been trained in the university phase of the program including 109 at Washington State University, 108 at the University of Idaho, 100 at Montana State University and 86 at the University of Alaska. Using 14 measures, including internal and external examinations, no significant differences in the performance of students have been found between the group beginning at each university phase site and those who began at home base in Seattle.[11]

- The WAMI program has trained 837 students and 180 residents in the community phase of the program, including 414 and 43, respectively, in family medicine; 62 and 71 respectively, in internal medicine; 148 and 55 respectively, in pediatrics; 49 and 9 respectively, in psychiatry, and 158 students and 2 residents in obstetrics and gynecology. Using multiple types of evaluations including part II of the National Boards and a comprehensive examination at the end of year III, no significant difference in performance was found in the subdisciplinary content areas between those students who had their basic clerkship experiences in the community phase of WAMI and those who had their experience in Seattle.[12]

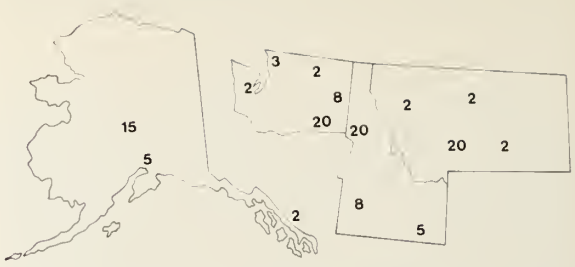

Figure 2.—The number of students assigned to the individual WAMI program sites in January 1979.

- Three family medicine community clinical units (CCU's) were closed because they no longer met program requirements. Six new units were opened, including family medicine units in Spokane, Washington; Pocatello, Idaho; Ketchikan, Alaska, and Anchorage, Alaska and Obstetric and Gynecology Units in Spokane and Anchorage. This has resulted in a total of 17 CCU's including seven in family medicine, one in psychiatry and three each in obstetrics and gynecology, pediatrics and internal medicine. At any one time, a total of 116 students out of a student body of 700 are receiving training in the university phase or the community phase of the program. (Figure 2).

- A total of 24.86 full-time equivalents (FTE) and 69 different faculty members are involved in the university phase of the program at sites remote to Seattle. In addition, 186 community-based faculty are involved in the community phase and hold clinical appointments in appropriate departments at the UWSM.

- Since 1975 faculty visits from the UWSM to each participating university have been made for the purpose of assisting in presenting courses at remote sites and helping to tie the regional system together. In addition to the "in-person" faculty visits, 120 faculty visits via satellite were made to the University of Alaska and Montana State University in the 1977-78 academic year and 120 are planned for the 1978-79 year. These satellite visits have involved full duplex audio and video interactive communication and have included the presentation of a nutrition course to students at the Fairbanks and Bozeman campuses,

as well as presenting enrichment experiments in the various courses.

- A total of 320 faculty visits from UWSM to CCU sites were conducted between 1975 and 1979. These faculty have presented continuing medical education courses to 12,800 attendees including physicians, nurses, physician extenders and other allied health professionals.
- It has been shown that 97 percent of the students involved in the university phase and 87 percent of the students involved in the community phase have been enthusiastic about the program (T. C. Cullen, M. R. Schwarz, unpublished data). Diminishing student concerns have been heard concerning the quality of the program, isolation, fairness, uneven treatment, equivalency of learning and social amenities.
- A longitudinal study of student career choices has been initiated designed to follow students for 25 years. Career preferences and expressions will be followed during medical school and residency training, and into active practice.
- A total of 108 faculty workshops, seminars and "specialty days" have been presented to the faculty in the WAMI program during the past four years, with an average attendance of 35. Some of these have been scheduled in conjunction with the Annual Faculty Retreat. In addition, 33 physician preceptorships and faculty exchanges have been arranged through the WAMI Office of Continuing Medical Education.
- Faculty performance evaluations have been provided by the Director of the WAMI program and the WAMI coordinators to appointments and promotions committees at the various universities. These have resulted in 21 faculty appointments or promotions for individuals involved in the WAMI undertaking.
- Each spring an annual WAMI faculty retreat is held involving university phase, community phase and University of Washington School of Medicine faculty members. The purpose of these retreats is to review the status of the program, resolve problems that have emerged, plan courses for subsequent years, share expertise and participate in continuing education in the form of speakers, panels and invited guests. Approximately 200 faculty attend these retreats, which have proven to be essential to the administration of this decentralized program.
- Minor curriculum modifications have been made including a change in credits format and hours of courses; developing common course objectives, contents, learning resources and evaluations, and the evolution of administrative procedures to govern the academic side of the program. The concept of "single courses taught at five sites by a single region-wide faculty" has been the guideline for curricular planning and implementation.
- No major new facilities have been added to the program, although the student study areas at Montana State University, the University of Idaho and the University of Washington have been remodeled and modernized. In addition, a building-remodeling program is being planned at Washington State University.
- The total costs of the WAMI program are now appropriated by the legislatures of the four WAMI states. Cost increases due to inflation have averaged 5 percent over the last three years and are projected at 9.1 percent in fiscal year 1980 and 6.0 percent in fiscal year 1981.
- In 1977 the WAMI program, along with the University of North Carolina Area Health Education Center (AHEC) system received the Richard and Hilda J. Rosenthal Award from the American College of Physicians for significant contributions to improving health care.
- Regional health educational programs have been or are being developed at the University of Washington School of Medicine in laboratory technology, physical and occupational therapy, and dentistry. In addition, there has been significant interest in developing similar programs in other parts of the country by various health disciplines including dentistry, medicine, podiatry, veterinary medicine, optometry and allied health professions. This has mirrored an intense interest in regional cooperation by public policy makers at state and national levels.
- In 1975 the WAMI program was reviewed by the Liaison Committee on Medical Education (LCME) and was granted full and unconditional accreditation for a seven-year period.

Program Outcomes

The WAMI program was established in 1971 to accomplish five goals:

1. Increase the number of students admitted to medical school from the states of Washington, Alaska, Montana and Idaho.

2. Increase the number of students being trained for careers in primary care, including

TABLE 1.—*Increase in the Number of Medical Students Under the WAMI Program.*

State	Admitted Pre-WAMI E63-E70	Admitted WAMI E71-E78	Average Number Students in Class 1963-70	Average Number Students in Class 1971-78	Percent Change
Washington	556	867	69.5	108.4	+56
Alaska	6	58	.75	7.25	+867
Montana	11	104	1.38	13.00	+845
Idaho	19	105	2.38	13.13	+453
Other states	71	66	8.88	8.25	−7
Total	663	1,200	82.88	150.00	+81

E=entering; for example, E63 indicates entering Fall 1963

TABLE 2.—*Increase in the Number of Primary Care Physicians*

	Entering 1970	Entering 1976	Percent Increase
Students in family medicine pathway	38	84	121.1
Students in clinical specialist pathway*	26	45	73.1
Students choosing primary care	64	129	101.1

*Number of students expressing career preference for primary care internal medicine or pediatrics.

TABLE 3.—*Location of Practices*

Population of Town/City	Non-WAMI Number	Non-WAMI Percentage	WAMI Number	WAMI Percentage
100,000+	138	50	27	33.7
10,000-100,000	74	26.8	21	26.3
1,000-10,000	38	13.8	28	35
Other	26	9.4	4	5
Totals	276	100	80	100

family medicine and primary care internal medicine and pediatrics.

3. Place physicians in areas of need.

4. Bring the resources of the Medical Center in Seattle to the communities throughout the four states that have need of them.

5. Accomplish the programmatic goals without new capital construction.

After seven years of programmatic activity, the following progress has been made on each of the goals.

Admissions

As can be seen in Table 1, there has been an 81 percent increase in the number of students admitted to the University of Washington School of Medicine since the WAMI program began. Included have been increases of 867 percent from the state of Alaska, 845 percent from the state of Montana, 453 percent from the state of Idaho and 56 percent from the state of Washington. Since these increases have been achieved without a change in the quality of the performance of these students, it is concluded that this goal has been achieved.

Primary Care

As may be seen in Table 2, there has been a 100 percent increase in the number of students choosing to enter primary care training pathways. This choice is first expressed at the end of the second year of the human biology curriculum and before students enter full-time clinical components of the curriculum. It is reaffirmed through a graduation questionnaire which is administered to all students at the time of graduation. It is significant that in addition to the 45 percent to 50 percent of each medical school class who choose careers in family medicine, another significant percentage choose the clinical specialist pathway and opt for careers in primary care internal medicine and pediatrics. Since these figures have now been observed for a period of four to five years, it is concluded that the second goal is being achieved.

Maldistribution of Physicians

While sufficient data are not available to draw firm conclusions relative to achievement of this goal, it is exciting to review the data that are available at present. It should be pointed out in this regard that access to the WAMI program can be obtained through two different methods. The first involves being a participant in the program in the university phase in the first year of undergraduate medical education and the second involves entering the program through its community phase as a house staff officer or resident. Since only nine university phase participants completed their undergraduate and graduate training, there are too few data to draw any conclusions relative to students who "entered the program" by the first route.

On the other hand, 80 residents have rotated through the community clinical units, completed their training and have practices (Table 3). A corresponding control group of 276 residents who have not rotated through the units have also begun practice. It is interesting to note a significant increase in the number of WAMI trainees who are choosing small towns for practice and a corresponding reduction in the number who are choos-

ing towns with populations greater than 100,000 people.

Resources to Community

The goal of bringing the resources of the Health Science Center in Seattle to communities which have need of them in the Pacific Northwest and Alaska has been implemented in the following way:

- *Faculty Visits*

In conjunction with the teaching program of the university phase and the required review and consultation in the community phase, routine faculty visits to the various program sites have been developed. In the 1977-78 year, 326 faculty visits were made to WAMI program sites. While reviewing the progress of students and residents, the faculty also act as special consultants to the practicing physicians in the area.

In addition, faculty presented 162 continuing education programs which have been attended by 3,412 health professionals. In some areas these visits have now been formalized into contracts with the communities in which the cost of the visits are paid for the practicing physicians in the communities which are served.

- *MEDCON*

The University of Washington School of Medicine, at the urging of Dean Dr. Robert L. Van Citters, established a regional medical consultation program called MEDCON. This telephone network allows a physician anywhere in the WAMI states (and Oregon) to call the University of Washington School of Medicine toll free and request consultation on patient problems. During the 1977-78 academic year, 9,332 calls were received from physicians in the four states. These calls, which represent virtually all subdisciplinary areas of medicine, have become progressively more numerous each year since the inception of MEDCON. For example, a 98 percent increase in calls was seen during 1977-78 as compared with 1976-77. All costs for MEDCON are assumed by the School of Medicine.

- *Satellite Communication*

Beginning in 1974 the University of Washington School of Medicine has conducted a series of experiments involving the use of highly advanced communication satellites. Both the ATS-6 satellite and the CTS satellites used in these experiments have had the technical capability of simultaneously transmitting two-way color television images and voice (full duplex audio video).

Among the experiments being conducted are those concerned with the admissions process, minority recruitment, faculty sharing (where faculty at the University of Washington present courses or course segments designed to enrich the curriculum at the peripheral sites), consultation process (where the clinical expertise of the Health Sciences Center is brought to bear on specific problems in the region) and independent learning (where the satellite has been used to determine to what extent travel can be replaced by this communication modality in the continuing medical education process). In all, nearly 350 broadcasts have been presented and the general conclusion has been reached that satellite communication has significant applications for health education and health care in the future.

- *Regional Orientation*

In addition to the decentralization of the WAMI program, other regionalized health services programs are developing at the University of Washington. Examples are the regionalized Physical and Occupational Therapy program, a Regional Dental Education program and a joint degree program involving the School of Public Health and two other institutions in the region.

Construction

While some remodeling has been done at various campuses to accommodate special curricular needs, no new buildings have been constructed to date in the WAMI program. Therefore, the goal of accomplishing the program's objectives without new capital construction has been achieved.

It is clear from the review of the goals of the WAMI program, that four of the five goals are being met and that the data on the remaining goal, offsetting the maldistribution of physicians, look very promising.

Future

In the future the evaluation of the WAMI program will continue with an eye toward demonstrating continued equivalence of learning, assessing faculty and student attitudes, documenting educational experiences in community clinical units and following students with a longitudinal study through at least 25 years of their careers. In addition, a regional network for graduate medical

education, which is tailored to the needs of the region and the training needs of the medical education network (including the needs of the hospitals which are involved), will most likely be developed. A similar continuing medical education network with decreased travel by the faculty and increased communication through telephone and satellite, may also be established. Finally, programs to sustain physicians who establish practices in the region may develop and most likely will be aimed at reducing the turnover of physicians observed in various communities. Such an activity could involve a cooperative arrangement between communities, the institutions of the region and the envisioned networks of undergraduate, graduate and medical education.

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Determining Hospital Test Accuracy

I THINK ONE always has to remember that what we say here coming from the university center and what you read in the journals may have no applicability to yourselves if, even though you have a test, you don't believe it or don't trust it. Then, performing it is of no value to you. So, no matter how good it may be in the literature, if it's not a good test in your hospital then obviously you have to use something else.

—THOMAS D. BOYER, MD, *San Francisco*

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Medical Information

Drug Choice for Treatment of Hypertension at 'Step 2'

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THE JOINT NATIONAL COMMITTEE on Detection, Evaluation, and Treatment of High Blood Pressure has recommended a "stepped care approach,"[1] initiating treatment with a small dose of an antihypertensive drug, increasing the dose of that drug and, as needed, adding other drugs. At *step 1* they recommend that a thiazide-type diuretic be prescribed. However, approximately 60 percent to 70 percent of hypertensive patients require a second drug at *step 2*.[2] The Committee suggests reserpine, methyldopa or propranolol hydrochloride, or a combination of these, as the second drug of choice.

The choice of drug at *step 2* is important for individual patients, and in a public health context as well. About 20 percent of adults in the United States have hypertension; consequently, in sheer numbers this is one of the most important drug choices that the physician makes.

Choice of a Step 2 Drug

Reserpine, methyldopa and propranolol appear to be equally effective. The most recent Veterans Administration Cooperative Study[3] concludes that "the reserpine-thiazide combination when subjected to controlled clinical trials has uniformly demonstrated antihypertensive effectiveness equal or superior to that of other antihypertensive agents." Unfortunately, this study did not concurrently compare the efficacy of reserpine with methyldopa-thiazide combinations. Smith and coworkers reported on a clinical trial in 1966 comparing these drugs in 189 patients and concluded that "neither alpha-methyldopa alone, in an average dose of 1.5 grams, or in combination with chlorothiazide, the latter at 1 gram daily, was as effective" as rauwolfia and chlorothiazide.[4] Other studies have shown no significant difference between the antihypertensive effects of reserpine and methyldopa.[5]

TABLE 1.—*Side Effects of Step 2 Antihypertensives*

Side Effects	*Methyldopa*	*Propranolol*	*Reserpine*
Depression	±	±	±
Abnormal liver function test	+	0	0
Chronic active hepatitis	+	0	0
Positive Coombs test	+ (20 percent)	0	0
Hemolytic anemia	±	0	0
Hypersensitivity, myocarditis, colitis	?	0	0
Nasal congestion	0	0	+
Bad dreams	+	+	+
Increased gastric acid	0	0	+
Bradyarrhythmia	0	+	±
Increased asthma	0	+	0
Heart failure	0	±	0
Impotence	+	±	?
Abnormal ejaculation	0	+	0

± = infrequent
+ = relatively common
0 = not reported

With no evidence of significantly greater antihypertensive effect of methyldopa, propranolol or reserpine, on what basis is a drug selected for a patient needing *step 2* medication? Criteria of importance to physician and patient include (1) frequency and seriousness of *side effects,* (2) cost, (3) number of tablets per day, (4) frequency of dosage and (5) significance of an omitted dose.

Side Effects

The major reason for the frequent avoidance of reserpine has been the possibility of provoking serious depressive reactions, including suicide. Textbooks and journals are literally crammed with warnings about this serious side effect with frequent statements that reserpine should not be used or used only with caution.

However, a careful review of the literature finds no evidence of a significantly high frequency of depression when reserpine is taken in therapeutic dosages (Table 1). In fact, reports of depression are based uniformly on clinical trials in which larger than therapeutic doses and, indeed, toxic doses of reserpine were administered. The article by Quetsch and associates,[6] itself a review of other studies on depressive reactions caused by reser-

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pine, shows that the doses ranged from a minimum of 0.4 mg up to 1.0 mg daily. Muller in 1955 described "severe mental illness" in 7.5 percent of patients receiving rauwolfia therapy.[7] The lowest dose in this series was 0.75 mg per day. Of the five patients who had such effects, three were receiving 2 mg or more per day, eight to ten times more than the therapeutic dose. Schroeder and Perry[8] described psychotic behavior with agitated depression states and suggested that doses were not abnormally high; in fact, all of the patients were taking at least 1 mg of reserpine daily.

Further review of the literature has *not* shown an incidence of depression from reserpine administration any greater than other antihypertensive drugs when therapeutic doses (that is, up to 0.25 mg a day) are used. For example, Gibb and associates[5] conducted a double-blind study of 60 matched hypertensive patients treated with bethanidine, alpha-methyldopa and reserpine; they showed that reserpine produced the *smallest incidence of side effects.* Further emphasizing the relative safety of reserpine were the Veterans Administration Cooperative Study Group reports on antihypertensive agents in 1962, 1967 and 1970, in which reserpine proved to be a consistently effective agent when combined with thiazide and was *no more toxic than other antihypertensive drugs.* The 1977 Veterans Administration study[1] compared various combinations of antihypertensive drugs and found that the combination of propranolol, thiazide and hydralazine, and the combination of reserpine and thiazide were most effective. The frequency of depression and lethargy were essentially *equal* in the propranolol-plus and the reserpine-plus groups. Reserpine provoked excessive side effects in comparison with the other drug combination *only* in the category of nasal stuffiness and, possibly, dyspnea, but *not in depression.*

Lassitude and somnolence are described in almost all reports on the side effects of alpha-methyldopa. (One wonders how carefully the differentiation is made between these symptoms and depression: When the patient reports "I have no energy and I feel low," which side effect is tabulated?) Positive Coombs tests are found in 20 percent of patients on a regimen of alpha-methyldopa but only in about 10 percent of this group do hemolytic anemia or thrombocytopenic purpura develop. However, as Böttiger and Westerholm[9] have pointed out, methyldopa is the leading cause of drug-induced hemolytic anemias (some 47 percent in their series), and, rarely, deaths have occurred. Methyldopa-induced hepatitis has been reported frequently.[10,11] Although the etiologic relationship is not certain, there have been recent reports of what appear to be methyldopa-induced myocarditis[12] and colitis. Impotence is another serious side effect not uncommonly described with alpha-methyldopa.

TABLE 2.—*Dosage and Cost of Step 2 Antihypertensives*

Factor	*Methyldopa*	*Propranolol*	*Reserpine*
Efficacy	Equal	Equal	Equal
Daily doses	3-4	2-4	1
Number of tablets daily	2-6	4-12	1
Effect of omitted dose	Significant	Significant	Minimal
Monthly cost	$12.00	$8.50	$.30

Propranolol is generally considered to be relatively free from disturbing side effects, but in the Veterans Administration Cooperative Study there was essentially no difference in frequency of lethargy, impotence, depression, headache, vertigo, ulcer symptoms and nightmares between reserpine-treated and propranolol-treated groups. Propranolol is frequently mentioned as a cause of congestive heart failure, but that appears to be rarer than had been expected. Bradyarrhythmias, bronchospasm in a patient with asthma and decreased adrenergic response to hypoglycemia in a diabetic patient receiving insulin are side effects that must be taken into consideration in deciding whether to use propranolol. In fact, bronchospasm occurs in 2 percent to 10 percent of patients, excluding those with asthma or previous bronchospasm.

Cost and Dosage

There are immense discrepancies among the costs of these medications (Table 2). Methyldopa will cost a patient at least 30 times as much as reserpine, and propranolol 25 times as much as reserpine, based on actual 1977 cost in a San Francisco outpatient department for a one month's supply at average dosages. This cost difference alone, in light of equal efficacy, is reason enough to seriously consider reserpine as the first drug to try at the *step 2* level. Obviously, the decision must be based on individual trials and consideration of the side effects of each drug.

Frequency of dosage and the number of tablets per day is less important than either side effects or cost; however, it is not unreasonable to assume that a patient is more likely to comply with a

therapeutic regimen if medication is required only once a day rather than three or four times per day. Reserpine should be prescribed only on a once per day basis. Propranolol is usually prescribed as four daily doses, although there is evidence suggesting that three, or perhaps even two, doses daily will maintain an antihypertensive effect.[13] Methyldopa is usually given three to four times a day; here also there is evidence that two doses a day are satisfactory and, in fact, one report indicates that once daily dosage is adequate.

Most patients using methyldopa take four to six tablets a day. A review of outpatient charts on patients taking methyldopa showed that some patients were given prescriptions for 8 to 12 tablets (250 mg tablets) per day. Propranolol is usually prescribed as 4 to 12 tablets daily. With reserpine, only one tablet per day should be taken.

It is probably an unusual patient who remembers to take every dose of prescribed medication. This is especially likely to be true in an asymptomatic condition such as hypertension. Because of long half-life (the slow disappearance of the antihypertensive effect) of reserpine, a missed dose has essentially no effect. The more rapid disappearance of antihypertensive effect of both propranolol[14] and methyldopa force a patient much more often to consider "Did I or did I not take my pill?"

Comment

Let us return to the hypothetical patient with essential hypertension that has not responded well to therapy with a thiazide diuretic. We now plan to take *step 2* in our treatment plan. From the above discussion, is there any reason to choose one drug over another? There is at present no overwhelming evidence that one is more or less efficacious than the other. Each of the three drugs has toxic side effects, but reserpine is "no more toxic than other antihypertensive drugs,"[3] and it seems clear that depression as a serious effect of reserpine has been overemphasized. As to frequency of dosage and number of tablets required per day, reserpine is clearly the preferable drug. It is likewise preferable in terms of its much longer half-life so that poor compliance has considerably less likelihood of having significant effect on the desired antihypertensive action. Finally, reserpine costs *between 25 times and 35 times less* than methyldopa and propranolol. Therefore, reserpine appears to be a reasonable first choice for most patients at *step 2* in the treatment of hypertension.

Summary

The Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure has recommended a "stepped-care approach," initiating treatment with a small dose of a thiazide-type diuretic, and, as needed, adding other drugs. In approximately 70 percent of hypertensive patients a second drug at *step 2* is required. The choice of the antihypertensive drug to be used at *step 2* is an important one. The recommended drugs—reserpine, alpha-methyldopa and propranolol—are compared on several bases. Reserpine appears to be a reasonable first choice for most patients at *step 2* in the treatment of hypertension.

Addendum

Since acceptance of this paper, F. A. Finnerty, Jr., MD; A. Gyftopoulos, MD; C. Berry, LPN, and A. McKenney, LPN have reported (JAMA 241: 579-581, Feb 9, 1979) a clinical trial comparing the *step 2* combination drugs of a thiazide plus either reserpine, methyldopa or propranolol. They also conclude that the reserpine-thiazide combination offers distinct advantages—on the same grounds as those outlined in this paper.

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Medical Information

New Approaches to Treatment of Back Pain

KATHLEEN M. WOOD, MD, *Denver*

LOW BACK PAIN is the most frequent presenting complaint in the Pain Clinic at the University of Colorado Medical Center. This is a discussion of an approach to its diagnosis and treatment.

Structure of the Lumbosacral Spine in Relation to Pain

For functional purposes, the spine is divided into two sets of "elements," anterior and posterior. The anterior elements are the vertebral bodies, discs, and their supporting muscles and ligaments; most important, the broad anterior longitudinal ligament running ventrally along the anterior surface of the bodies and the narrow posterior longitudinal ligament running along the dorsal surface of the bodies in the neural canal. The posterior elements make up the neural arch—the pedicles, the laminae, transverse and spinous processes, the facet joints and their supporting muscles and ligaments, including the ligamentum flavum running along the roof of the neural canal from neural arch to neural arch. The cauda equina begins at L-1. Like a telephone cable, that which is the most central travels the furthest, so the sacral roots lie in the center and the lumbar roots are the most peripheral. These roots are contained within the dura.

The anterior elements are designed for weight-bearing and have minimal sensory innervation. There are nerve fibers in the periosteum of the vertebral bodies, the anterior and posterior longitudinal ligaments, and superficially in the annulus fibrosus. The posterior elements serve the purpose of preventing excessive movements of the spine, thereby protecting the contents of the neural canal. They are innervated by the first branch off the segmental nerve as it leaves the vertebral foramen.

Injections of hypertonic saline[1] down to the ligamentum flavum yield localized pain, while injections of the longitudinal ligaments and the ligamentum flavum itself cause a diffuse, dull low back pain radiating into the hips. Injections into facet joints, annulus fibrosus and nucleus pulposus yield typical sciatic pain, but the distribution of that pain does not necessarily correlate with the area injected.

The precise diagnosis of the source of anyone's backache, therefore, is enigmatic. At autopsy, examination of the lumbar spine shows degenerative changes in 100 percent of those middle-aged or older.[2] However, the severity of the anatomical process does not correlate with the complaints of the living owner of the back.

In the overall structure of the back, the weak link is the disc. While the disc itself may not be the source of pain, the degenerative process begins with the disc and centers around it. The first two discs to go are the ones at the bottom of the pile, the L4-5 and the L5-S1. The disc loses its blood supply in early childhood, and thereafter depends on passive diffusion of fluid to maintain its turgor. Gravity compresses it during at least two thirds of each day. With age, the nucleus changes from liquid gel to granular solid, while the annulus begins to develop radial cracks, especially posteriorly, where the lumbar lordosis compresses most. Anterior bulging of the annulus, pressing against the anterior longitudinal ligament, lifts the ligament off the body of the vertebra, causing irritation and possibly some bleeding with osteogenic organization of the space created, so that anterior "lipping," and even "bridging" of the vertebral bodies shows on x-ray studies.

Posterior bulging of the annulus impinges on the posterior longitudinal ligament. As a radial crack enlarges, the nucleus pulposus can ooze through it laterally to compress a nerve root passing through its foramen, with resultant sciatica. If compression is central on the cauda equina, it affects sacral nerve roots, with resultant bladder and bowel symptoms. The nucleus in some patients is so isolated from the circulation of the rest of the body that it actually becomes a foreign body, behaving somewhat like an antigen; consequently when it is released into the epidural space a severe inflammatory reaction can result.

From the Department of Anesthesiology, University of Colorado Medical Center, Denver.

Reprint requests to: Kathleen M. Wood, MD, Dept. of Anesthesiology, University of Colorado Medical Center, 4200 East 9th Avenue, Denver, CO 80262.

As the interbody space narrows, the facet joints, whose teleological purpose is to prevent excessive flexion, extension or rotation of the spine, become weight-bearing joints. Since these joints have complete innervation, they respond to weight-bearing with pain; just as finger joints would, if they were obliged to bear weight.

Sciatica is low back pain radiating down to one or both legs. It can be caused by nerve root irritation: the impingement of a herniated nucleus pulposus; the compression by an overhanging, hypertrophied, arthritic facet joint, or the tugging of adhesions resulting from surgical operation or from arachnoiditis after a myelogram. There is one case report of this kind of pain in a patient in whom a blood patch was done to eliminate a spinal headache. Facet joint pain is also sciatic in nature, but typically radiates no farther than the knee. Unfortunately the sciatic distribution does not identify which joint is involved. There may also be some loci of ligamentous irritation that can cause sciatica.

Lumbago is low back pain without leg radiation. It commonly spreads across the sacroiliac area, causing gluteal spasm and hip pain. Ligamentous irritation in the lumbar spine is far more common as a cause of sacroiliac pain than is the sacroiliac joint itself. The symptoms of lumbago can be produced by injecting hypertonic saline into the interspinous ligament, the ligamentum flavum and the posterior longitudinal ligament.

Natural History of Low Back Pain

Eighty percent of human adults will experience low back pain in their lifetimes.[3] Backache is an episodic, recurring phenomenon. It is age-related, beginning with low frequency in the 20's, gradually increasing in both frequency and severity in the 30's and 40's, declining in the 50's and disappearing in the 60's, at which age the lumbar segment is likely to achieve a spontaneous fusion. Complaints from this benign condition usually begin early, so the patient whose symptoms begin in his 50's should be studied for tumor and infection,[4] although the odds are about 9:1 that his problem will also be benign.

The following are outcomes in patients with an episode of back pain but without previous surgical therapy:

- 60 percent recover in three weeks, regardless of therapy;
- 90 percent recover in two months, regardless of therapy;
- 50 percent will have recurrences of the condition eventually;
- 12 percent (approximately) will prove to have a herniated nucleus pulposus.[3]

Therapeutic Modalities and Results

Knowing that most backaches are going to get better anyway, one begins with conservative therapy.[5] This consists of bed rest, traction and use of the various sedative drugs that are called muscle relaxants. If this fails, the patient moves to exercises designed to strengthen the abdominal muscles, flatten the lumbar lordotic curve, and loosen the hamstrings and the paraspinous muscles.

For a number of years lumbar pain has been treated with the "steroid epidural." This involves positioning a needle in the epidural space, injecting about 5 ml of a local anesthetic to eliminate the slight burning sensation caused by the steroid, and then administering 80 mg of methylprednisolone suspension or 50 mg of triamcinalone. If the patient has sciatic pain, the interspace that is closest to the distribution of the pain should be selected. Therefore, if the radiation is to the medial aspect of the knee, that is probably L-4, indicating the L4-5 interspace. If the radiation is to the great toe, that is L-5, indicating either L4-5 or L5-S1. If the radiation is to the lateral toes, that is S-1, and the L5-S1 interspace should be chosen.

There is a very limited follow-up available on this form of therapy. A recent study from the University of Virginia[6] suggests that all patients, whether or not they have had surgical therapy, yield about a 40 percent subjective improvement rate. This is remarkably good for pain clinic patients. Thirty percent reduced their drug intake, which is not so impressive. Of the total group, 80 percent did not go on for more surgical therapy than they had already had, but this is almost meaningless because by the time patients reach the pain clinic they have already given up on surgical operations or have been refused further operations. There is an impression that previous operations reduce the likelihood of favorable response to a steroid epidural, but results of the study from Virginia (which included patients who had had operations previously) do not seem to bear that out; the procedure therefore, seems like a worthwhile thing to try. Steroid epidural seems to work well on patients who have facet joint pain or ligamentous irritation.

For a patient who may have nerve roots

bound down by epidural adhesions after an operation, or by subarachnoid adhesions after a myelogram, there is another anesthetic procedure, the "flexion spinal," consisting of a spinal anesthetic up to about a T-8 sensory level. When anesthesia is achieved, the patient's knees are moved up toward his chest gently but firmly. If there is no resistance as the knees approach the chest, there probably are no nerve root adhesions. When they exist, there will be resistance as the knees approach the chest. There should then be a gradual "give," and at that point the patient will say he has a peculiar feeling in his neck. It is a fairly vigorous maneuver to do to a patient, but once the adhesions are released the nerve root is free to go through its normal excursion in the intervertebral foramen. During this maneuver nerve roots normally travel an estimated one centimeter in the intervertebral foramen. After treatment the patient must faithfully do daily flexion exercises (bringing knees to chest) in order to walk with a normal stride, pain-free. There are no statistics as to the results. For a few patients with this problem it has been very helpful. The danger is tearing a nerve root instead of an adhesion, and so the patient must be warned that some new numb spots may develop in a leg, since the posterior nerve roots are the most stretched and most likely to be torn. Otherwise the complications are only those of a spinal anesthetic.

Another relatively conservative form of treatment that has appeared in recent years is done by neurosurgeons with a heat-generating probe. They place this over the facet joint, and allow it to warm up to the point where it can cause a small lesion in the area above the facet joint. This is presumed to destroy the small nerve that serves that facet joint, and by denervating it interrupts the pain pathway. In patients who have not had operations this is about 50 percent effective, and for a pain clinic population that result is extremely good.[7] Patients who have had operations previously can expect only a 26 percent chance of good results. The Neurosurgery Department of the University of Colorado reports an overall average of 20 percent good results,[8] but has noted that if the patients are unemployed, even if they report some pain relief they do not return to work.

As far as operative treatment goes, excision of a disc is only effective in the case of a true herniated nucleus pulposus. Removing part of a bulging annulus fibrosus does not help, and it can increase the pain by increasing facet joint compression. The patient who has a true herniated disc will benefit from surgical therapy, but should be warned in advance that even though the sciatica will go away the lumbago is likely to remain.[9] In patients with hard neurological findings and positive myelograms, a surgical operation should be done.

Numerous papers have been published on the results of surgical therapy, and even that approach is a discouraging proposition.[9-13] Those who become pain-free and return to their original work make up about 10 percent to 30 percent of cases in which operations were done; in 75 percent there is relief of sciatic but some residual lumbago-type pain. This is a consistent finding in almost all of the papers published. Failure to improve applies to 10 percent to 21 percent of all patients in whom operations are done.

The results of second and third operations (and some patients have many more) are very discouraging, no matter what is done. If the operation is merely a lysis of adhesions, there is 100 percent long-term failure.[3] For a while it was thought that dorsal rhizotomies in painful segments might help, and there were widely varying reports of success. Fifteen percent appears to be the most reasonable expectation of pain relief from rhizotomy.[3] This author was unable to find any figures for reoperation with excision of new herniation at the same or a different level, or for spinal fusion as a separate second operation. In overall reports that do not distinguish the type of operative procedure, after second back operations two thirds of all patients remain the same or get worse.

Chymopapain for disc injection has been withdrawn from the market. Its success rate was reported as 50 percent, but its complication rate, including anaphylaxis and local inflammatory processes, was too high.

Low back pain is a benign disease, but it is a malignant social problem. In England the man-days lost from work because of low back pain are about 3.6 percent of the total of all days lost. This amount of time exceeds all the man-days lost in strikes. In Sweden's employed population, 4.4 percent of men and about 3.9 percent of women are away from work in any one year with complaint of low back pain, and most of these absences last longer than three weeks.[14,15] In the United States a report dealing with the 13 western states shows that the primary reason for hospital admissions covered by workers' compensation programs was low back pain.[3] It is the most expensive ailment treated in California.[3]

In Colorado every worker's backache costs the compensation fund $800 for medical care and time away from work. This does not include payments made on a permanent basis for disability. Five percent of all Workman's Compensation claims in Colorado are due to low back pain, as are more than 50 percent of all claims that run for more than one year, according to Mr. C. McGrath, Assistant Manager of the Colorado State Compensation Insurance Fund (personal communication, July 1977).

There are a few misconceptions about who gets low back pain that need correcting: it afflicts men and women equally. It afflicts white collar workers and laborers to an equal extent, although the latter are more likely to be disabled by it.[3] Its frequency is strongly related to age. It is not related to height or weight. It is more frequent in divorced or single men than in married men, and is more frequent in poorer people.[16] By the time they reach a pain clinic, a substantial number are "low back derelicts."[17] That is, they have been unemployed for more than two years, or if female, they have not been doing the housework for more than two years, and have had one or more operations. Of these low back derelicts, 80 percent are male, 65 percent are in the age range of 30 to 49 years old, 56 percent were injured on the job, 100 percent are drug addicted, 100 percent deny drug abuse, 67 percent are abusing alcohol as well, and by this time 78 percent are obese. Psychologically they are dependent, hypochondriacal, sometimes psychopathic and almost always depressed.[17]

A study conducted in California[17] studied 79 low back derelicts. These patients were put into an intensive rehabilitation program. Their previous total cost to various insurance programs and the state of California had been more than $500,000. After this intensive program, consisting of psychotherapy, vocational rehabilitation counseling, physical conditioning and reduction of drug use, not one went back to work.

This type of program, called the "behavioral training approach," is the latest method of treatment,[18] and the one that seems the most promising in dealing with pain problems of several years' duration. It includes a graded increase in physical activity. The patient is admitted to a ward where he is obliged to get up, make his bed, go to a common place to have his meals and then to go work at his physiotherapy. He is obliged to keep a chart above his bed of the amount of time that he spends out of it and the amount of time that he spends doing what he is supposed to do in terms of exercises and activities. He is encouraged to behave like a healthy man, or she like a healthy woman. If the patient tries to complain about pain, the nurse approached will just quietly walk away. Pain complaints are resolutely ignored; more cheerful and outgoing behavior is thoroughly encouraged. The patient will get vocational counseling while in this program. His family will be brought in and taught how to encourage him to be more active, and how to discourage him from acting like a sick person. He will also undergo gradual drug withdrawal during this time. At the end of the usual six week hospital course, the results sometimes seem almost miraculous. But if success rate is to be judged by whether the patient returns to work, this approach is a failure, too. However, the patient is better adapted, is easier for his family to live with and is therefore less likely to be turned out of the home as a derelict alcoholic.

There are a number of centers around the United States that provide this kind of care. They can be located through the American Society of Anesthesiologists' *Pain Clinic Directory*.* Some state workers' compensation funds and many private insurance companies, will cover the cost. Since it is a relatively new concept, a patient needs to check with the carrier before admission. Cost-effectiveness would be unquestionable if the patients regularly returned to work. But it is still cost-effective when it forestalls further hospital admissions for work-up, surgical operations and treatment of the complications of drug abuse.

Patients with low back pain often shop around the medical world, convinced that if they can only find the right doctor, the right diagnosis will be made and the right treatment will be given. Many also are convinced that all preceding doctors have misdiagnosed and mistreated them. The first doctor to see such a patient must reassure him that he has a common problem, that it will come and go, and that if it is not relieved by a reasonable period of rest and conservative treatment, and is still plainly not due to a herniated nucleus pulposus, then the patient himself must assume the greater responsibility for his betterment: working at his own physical conditioning, losing weight if necessary, limiting his drug intake and not allowing the problem to dominate his life.

*American Society of Anesthesiologists 515 Busse Highway, Park Ridge, IL 60068.

Conclusion

Benign low back pain is an intermittent, relapsing disorder based upon the inevitable degeneration of the intervertebral disc. We are only in the early stages of understanding it and treating it appropriately.

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—THEODORE R. MILLER, MD, *New York City*
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in memoriam

ABBOTT, GORDON ARTHUR, San Jose. Died January 26, 1979 in Fresno of cerebrovascular accident, aged 79. Graduate of Northwestern University Medical School, Chicago, 1930. Licensed in California in 1953. Dr. Abbott was a retired member of the Santa Clara County Medical Society.

BRODE, WILLIAM RICHARD, Richmond. Died March 4, 1979 in South Lake Tahoe, aged 61. Graduate of McGill University Faculty of Medicine, Montreal, 1943. Licensed in California in 1947. Dr. Brode was a member of the Alameda-Contra Costa Medical Association.

FISHBON, HARRIS M., San Francisco. Died February 13, 1979 in San Francisco, aged 70. Graduate of the University of California Medical School, Berkeley-San Francisco, 1933. Licensed in California in 1933. Dr. Fishbon was a member of the San Francisco Medical Society.

HALL, CHARLES C., Oakland. Died January 28, 1979 in Walnut Creek, aged 85. Graduate of Harvard Medical School, Boston, 1921. Licensed in California in 1925. Dr. Hall was a retired member of the Alameda-Contra Costa Medical Association.

HOUGH, RIETA CAMPBELL, San Diego. Died February 9, 1979 in San Diego, aged 87. Graduate of the University of Oregon Medical School, Portland, 1923. Licensed in California in 1925. Dr. Hough was a retired member of the San Diego County Medical Society.

KLOTZ, ADDIE L., Los Angeles. Died March 3, 1979 in Northridge of cancer, aged 51. Graduate of Western Reserve University School of Medicine, Cleveland, 1958. Licensed in California in 1959. Dr. Klotz was an associate member of the Los Angeles County Medical Association.

LEONARD, MAURICE E., San Francisco. Died February 19, 1979 in San Francisco of heart disease, aged 72. Graduate of McGill University Faculty of Medicine, Montreal, 1932. Licensed in California in 1933. Dr. Leonard was a member of the San Francisco Medical Society.

MAISLER, SOL, San Francisco. Died February 5, 1979 in Stockton, aged 74. Graduate of the University of California Medical School, Berkeley-San Francisco, 1928. Licensed in California in 1928. Dr. Maisler was a retired member of the San Francisco Medical Society.

MITCHELL, EDWARD, La Jolla. Died January 26, 1979 in La Jolla, aged 67. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1939. Licensed in California in 1939. Dr. Mitchell was a retired member of the San Diego County Medical Society.

MORGAN, LOUIS S., Long Beach. Died August 17, 1978 of heart disease, aged 81. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1921. Licensed in California in 1946. Dr. Morgan was a member of the Los Angeles County Medical Association.

NEHRING, JAMES R., Pomona. Died January 15, 1978 of myocardial infarction, aged 43. Graduate of State University of New York, Downstate Medical Center, College of Medicine, 1966. Licensed in California in 1967. Dr. Nehring was a member of the Los Angeles County Medical Association.

NEWLIN, WILLARD S., Brea. Died August 11, 1978 of heart disease, aged 60. Graduate of State University of Iowa College of Medicine, Iowa City, 1946. Licensed in California in 1949. Dr. Newlin was a member of the Orange County Medical Association.

NIEBEL, HERBERT L., Palo Alto. Died February 24, 1979 in Mountain View, aged 87. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1923. Licensed in California in 1923. Dr. Niebel was a member of the Santa Clara County Medical Society.

SHERANIAN, HEROND N., Los Angeles. Died April 9, 1978, aged 85. Graduate of Long Island College of Medicine, New York City, 1919. Licensed in California in 1930. Dr. Sheranian was a member of the Los Angeles County Medical Association.

TRINITY, GRANVILLE J., Glendale. Died June 23, 1978, aged 65. Graduate of Wayne University College of Medicine, Detroit, 1937. Licensed in California in 1943. Dr. Trinity was a member of the Los Angeles County Medical Association.

WEINSTEIN, MORTON R., San Francisco. Died March 5, 1979 in San Francisco, aged 48. Graduate of Cornell University Medical College, New York City, 1955. Licensed in California in 1956.

Correction: In the January 1979 In Memoriam section, the information given for Dr. Arthur R. Roberts was incorrect. The notice should have read as follows:

ROBERTS, ARTHUR R., Fullerton. Died September 24, 1978, aged 50. Graduate of the University of Southern California School of Medicine, Los Angeles, 1954. Licensed in California in 1955. Dr. Roberts was a member of the Orange County Medical Association.

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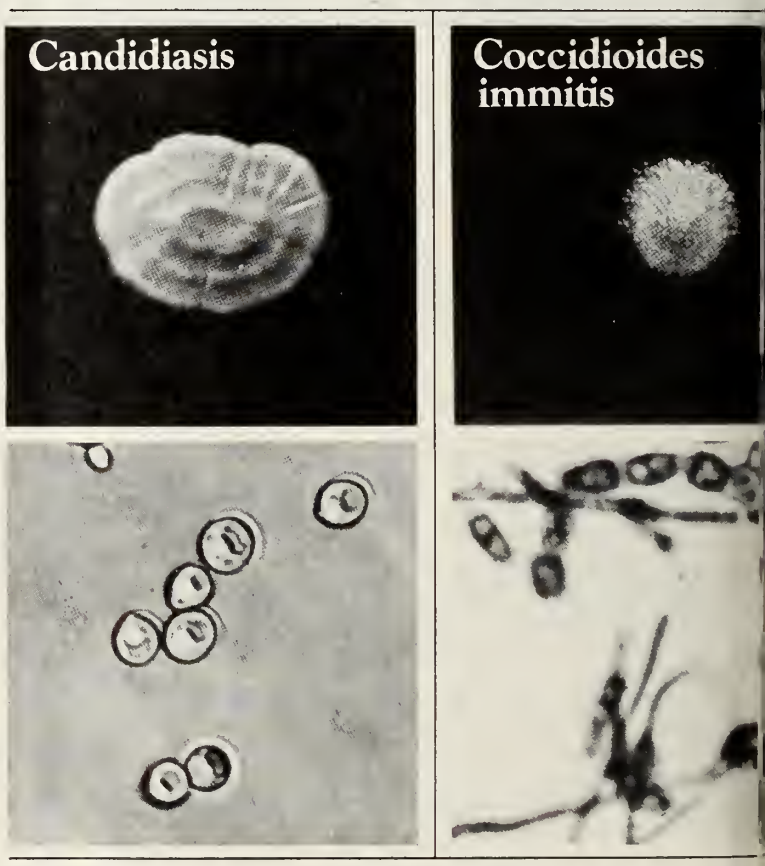

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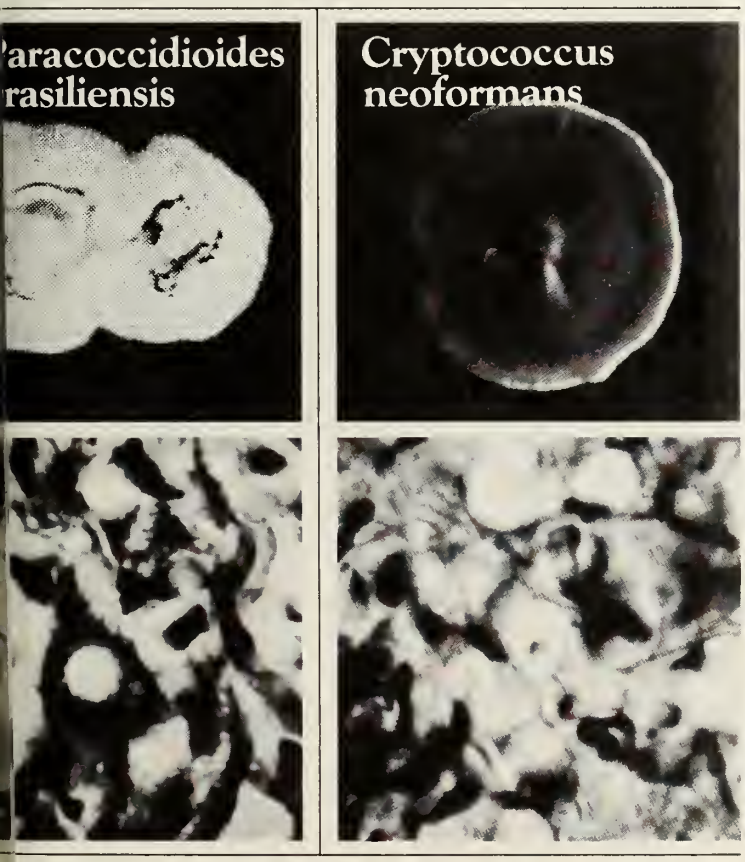


generally well tolerated by severely debilitated patients

- cancer patients
- patients receiving immunosuppressive drugs
- patients with serious underlying conditions such as renal insufficiency or diabetes mellitus

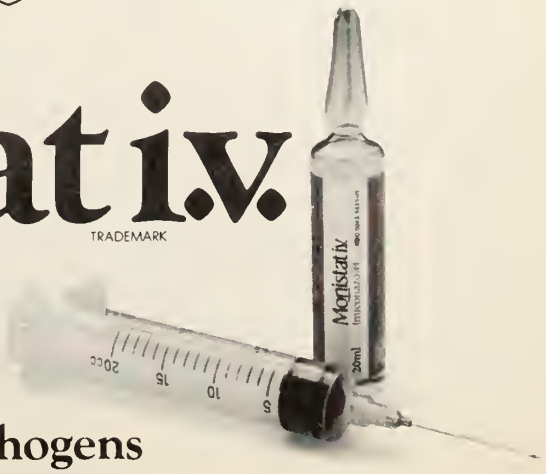
for more information

Because of the uniqueness of new MONISTAT i.v. only some of the highlights can be presented in this advertisement. For more information, i.e., product monograph, dosage schedules, etc., please fill out the coupon on the next page and mail to Ortho Pharmaceutical Corporation.

Please turn page for Prescribing Information

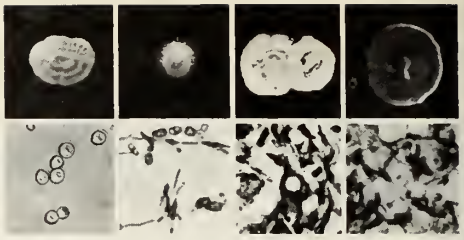
Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

new Monistat i.v.
TRADEMARK
(miconazole)



broad-spectrum activity against major systemic fungal pathogens

in systemic fungal infections...



new Monistat i.v. (miconazole)

TRADEMARK

a broad-spectrum systemic antifungal agent

DESCRIPTION: MONISTAT i.v. (miconazole) 1-{2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl) methoxyl ethyl} 1 H-imidazole is a synthetic antifungal supplied as a sterile solution for intravenous infusion. Each ml of this solution contains 10 mg of miconazole with 0.115 ml PEG 40 castor oil, 1.0 mg lactic acid USP, 0.5 mg methylparaben USP, 0.05 mg propylparaben USP in water for injection. Miconazole i.v. is a clear, colorless to slightly yellow solution having a pH of 3.7 to 5.7.

CLINICAL PHARMACOLOGY: MONISTAT i.v. is rapidly metabolized in the liver and about 14% to 22% of the administered dose is excreted in the urine, mainly as inactive metabolites. The pharmacokinetic profile fits a three-compartment open model with the following biologic half-life: 0.4, 2.1, and 24.1 hours for each phase respectively. The pharmacokinetic profile of MONISTAT i.v. is unaltered in patients with renal insufficiency, including those patients on hemodialysis. The in vitro antifungal activity of MONISTAT i.v. is very broad. Clinical efficacy has been demonstrated in patients with the following species of fungi: *Coccidioides immitis, Candida albicans, Cryptococcus neoformans, and Paracoccidioides brasiliensis.*

Recommended doses of MONISTAT i.v. produce serum concentrations of drug which exceed the in-vitro MIC values for the fungal species noted above. Doses above 9 mg/kg of MONISTAT i.v. produce peak blood levels above 1 μg/ml in most cases. The drug penetrates into joints.

INDICATIONS: MONISTAT i.v. is indicated for the treatment of the following severe systemic fungal infections: coccidioidomycosis, candidiasis, cryptococcosis, paracoccidioidomycosis, and for the treatment of chronic mucocutaneous candidiasis. However, in the treatment of fungal meningitis and urinary bladder infections an intravenous infusion alone is inadequate. It must be supplemented with intrathecal administration and bladder irrigation. Appropriate diagnostic procedures should be followed and MICs should be determined.

MONISTAT i.v. should not be used to treat common trivial forms of fungal diseases.

CONTRAINDICATIONS: MONISTAT i.v. is contraindicated in those patients who have shown hypersensitivity to it.

WARNINGS: Rapid injection of undiluted MONISTAT i.v., may produce transient tachycardia or arrhythmia.

PRECAUTIONS: Before a treatment course of MONISTAT i.v. is started, the physician should make sure that the patient is not hypersensitive to the drug product. MONISTAT i.v. should be given by intravenous infusion. The treatment should be started under stringent conditions of hospitalization but subsequently may be given to suitable patients under ambulatory conditions with close clinical monitoring. It is recommended that an initial dose of 200 mg be given with the physician in attendance. It is also recommended that clinical laboratory monitoring including hemoglobin, hematocrit, electrolytes and lipids be performed.

It should be borne in mind that systemic fungal mycoses may be complications of chronic underlying conditions which in themselves may require appropriate measures.

Pregnancy: Reproductive studies with MONISTAT i.v. in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus. There are no data, however, on the use of the drug in pregnant women.

Children: Since the safety of miconazole i.v. in children under one year of age has not been extensively studied, its benefits in this age group must be weighed against the possible risks involved.

ADVERSE REACTIONS: Adverse reactions which have been observed with MONISTAT i.v. therapy include phlebitis, pruritus, rash, nausea, vomiting, febrile reactions, drowsiness, diarrhea, anorexia and flushes. In the U.S. studies, 29% of 209 patients studied had phlebitis, 21% pruritus, 18% nausea, 10% fever and chills, 9% rash, and 7% emesis. Transient decreases in hematocrit and serum sodium values have been observed following infusion of MONISTAT i.v. Thrombocytopenia has also been reported. No serious renal or hepatic toxicity has been reported. If pruritus and skin rashes are severe, discontinuation of treatment may be necessary. Nausea and vomiting can be mitigated with antihistaminic or antiemetic drugs given prior to MONISTAT i.v. infusion, or by reducing the dose, slowing the rate of infusion, or avoiding administration at mealtime.

Aggregation of erythrocytes or rouleau formation on blood smears has been reported. Hyperlipemia has occurred in patients and is reported to be due to the vehicle, Cremophor EL (PEG 40 castor oil).

DRUG INTERACTIONS: Drugs containing cremophor-type vehicles are known to cause electrophoretic abnormalities of the lipoprotein. These effects are reversible upon discontinuation of treatment but are usually not an indication that treatment should be discontinued.

Interaction with the coumarin drugs resulting in an enhancement of the anticoagulant effect has also been reported. In cases of simultaneous treatment with MONISTAT i.v. and coumarin drugs, the anticoagulant effect should be carefully titrated since reductions of the anticoagulant doses may be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE

Adults. The doses may vary with the diagnosis and with the infective agent, from 200 to 1200 mg per infusion. The following daily doses, which may be divided over 3 infusions, are recommended.

Organism	Dosage Range*	Duration of Successful Therapy (weeks)
Coccidioidomycosis:	1800 to 3600 mg per day	3 to > 20
Cryptococcosis:	1200 to 2400 mg per day	3 to > 12
Candidiasis:	600 to 1800 mg per day	1 to > 20
Paracoccidioidomycosis:	200 to 1200 mg per day	2 to > 16

* May be divided over 3 infusions.

Repeated courses may be necessitated by relapse or reinfection.

Children: A total daily dose of about 20 to 40 mg/kg is generally adequate. However, a dose of 15 mg/kg body weight per infusion should not be exceeded.

ADMINISTRATION: MONISTAT i.v. should be diluted in at least 200 ml of fluid. The diluent of choice is 0.9% sodium chloride or alternatively Dextrose 5% injectable solution. The intravenous infusion should be given over a period of 30 to 60 minutes.

Generally, treatment should be continued until all clinical and laboratory tests no longer indicate that active fungal infection is present. Inadequate periods of treatment may yield poor response and lead to early recurrence of clinical symptoms. The dosing intervals and sites and the duration of treatment vary from patient to patient and depend on the causative organism.

OTHER MODES OF ADMINISTRATION: Intrathecal. Administration of the undiluted injectable solution of MONISTAT i.v. by the various intrathecal routes (20 mg per dose) is indicated as an adjunct to intravenous treatment in fungal meningitis. Succeeding intrathecal injections may be alternated between lumbar, cervical, and cisternal punctures every 3 to 7 days. Bladder instillation of 200 mg of diluted solution is indicated in the treatment of mycoses of the urinary bladder.

HOW SUPPLIED: MONISTAT i.v. is supplied in 20 ml ampoules.

MONISTAT i.v. (miconazole) is an original product of Janssen Pharmaceutica N.V., Belgium, and co-developed by Ortho Pharmaceutical Corporation.

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

WJ4/79

Ortho Pharmaceutical Corporation
c/o 733 Summer Street
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Please send me more information on the new broad-spectrum, systemic antifungal agent...MONISTAT i.v. (miconazole).

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October 1978

ORAL HYDERGINE® TABLETS, 1 mg (1 tab t.i.d.)

Each 1-mg Hydergine tablet contains dihydroergocornine mesylate 0.333 mg, dihydroergocristine mesylate 0.333 mg, and dihydroergocryptine (dihydro-alpha-ergocryptine and dihydro-beta-ergocryptine in the proportion of 2:1) mesylate 0.333 mg, representing a total of 1 mg.

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Indications: Selected symptoms in elderly patients, such as mood-depression, confusion, unsociability, dizziness, and lack of self-care, of unknown etiology.
Contraindications: Hypersensitivity to the drug
Precautions: *Because the target symptoms are of unknown etiology, careful diagnosis should be attempted before prescribing Hydergine tablets and sublingual tablets.*
Adverse Reactions: Serious side effects have not been found. Some sublingual irritation, transient nausea, and gastric disturbances have been reported. Hydergine tablets and sublingual tablets do not possess the vasoconstrictor properties of natural ergot alkaloids.
Dosage and Administration: 1 mg three times daily. Alleviation of symptoms is usually gradual and results may not be observed for 3–4 weeks.
How Supplied: Hydergine tablets (for oral use) 1 mg, packages of 100 and 500. **Hydergine sublingual tablets 1 mg,** containing dihydroergocornine mesylate 0.333 mg, dihydroergocristine mesylate 0.333 mg, and dihydroergocryptine (dihydro-alpha-ergocryptine and dihydro-beta-ergocryptine in the proportion of 2:1) mesylate 0.333 mg, representing a total of 1 mg, packages of 100, 500, and 1000. **Hydergine sublingual tablets 0.5 mg,** containing dihydroergocornine mesylate 0.167 mg, dihydroergocristine mesylate 0.167 mg, and dihydroergocryptine (dihydro-alpha-ergocryptine and dihydro-beta-ergocryptine in the proportion of 2:1) mesylate 0.167 mg, representing a total of 0.5 mg; packages of 100 and 1000.
Before prescribing, see package insert for full product information.

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DIRECTOR, FAMILY PRACTICE PROGRAM. Opportunity to implement own ideas in teaching and administration. Program is part of the University of California, Davis, Family Practice Network. Faculty appointment, competitive salary and benefits; Board Certification by ABFP required. Practice and teaching experience desirable. Send curriculum vitae to: L. Thomas Fife, MD, Associate Director, Family Practice Residency Program, Merced Community Medical Center, PO. Box 231, Merced, CA 95340.

PRIMARY CARE INTERNIST sought for full-time faculty position. Community Hospital based Family Practice Residency Program. Board Eligibility required. Practice 40 percent, Teach 60 percent. Excellent salary and fringe benefits. Affiliated with UCLA. Direct inquiries and forward CV to William F. Walsh, MD, Program Director, 1620 West Ave J, Lancaster, CA 93534.

ADULT PHYSICIAN: Gardner Community Health Center. To provide primary medical care, prenatal care to low income community. $2,265/m start to $3,000/m after 3 months. Exclt benefits. Contact Mary Rose at (408) 998-2264.

FAMILY PRACTICE RESIDENCY DIRECTOR: Opportunity to implement own ideas in teaching and administration. Program is part of the University of California, Davis, Family Practice Network. Faculty appointment, competitive salary and benefits: Board certification by ABFP required; practice and teaching experience desirable. Send curriculum vitae to: L. Thomas Fife, MD, P.O. Box 231, Merced Community Medical Center, Merced CA 95340. (209) 723-0444.

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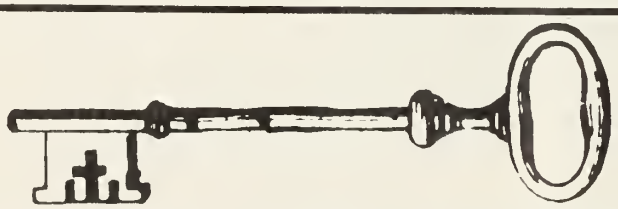
(Continued on Page 31)



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(Continued from Page 28)

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(Continued from Page 31)

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RADIOLOGIST—Northern California busy two-office practice. Must be good in ultrasound. Attractive compensation and time off. Write Box 6036, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

SITUATIONS WANTED

PHYSICIAN with 10 years experience in preventive and occupational medicine and postgraduate training for 4 years, seeks position in San Francisco/Bay Area in medical outpatient clinic. Write Box 6020, The Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

PEDIATRICIAN—32, board certified, California license. Wishes to join a group practice in Bay area. Excellent training and experience, personable. Write Box 6028, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ABIM, age 33, finishing infectious disease fellowship summer 1979. Seeks group or hospital based practice, would welcome association with microbiology laboratory and/or house staff program. Write Box 6032, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

DIAGNOSTIC RADIOLOGIST with 20 years experience seeks group affiliation. Prefer location out of large metro areas. Box 6024, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

INTERNIST with industrial and private practice experience available for full or part-time position. Write Box 9037, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

EXPERIENCED PA-C wants to relocate to Pacific NW. Currently employed X 2 yrs as director and primary provider in rural satellite clinic seeing all phases of gen. pract. Also ER experience. Looking for solo/small group setting. Available August 1979. Contact Steven Meltzer, Rt. 1, Box 141, Atkinson, NC 28421. (919) 283-7701 home or 283-7783 work.

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OREGON CLINIC for Lease or Sale, suitable for Physicians Group, Dental Center, Research or Health Spa. Building has 14 rooms, commercial kitchen, nurses station, plenty of parking area for patients and staff on ¾ acre, in quiet area, opposite beautiful golf course. Vacant now. 38 miles Portland, 26 miles Salem. Mrs. Moore, P.O. Box 92, McMinnville, OR 97128. Telephone (503) 472-8825.

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PHYSICIAN, FAMILY PRACT. DISABLED. For Sale/Lease, Gross $76,000 in '78. Office, 6 rooms, x-ray, hosp. available. Fred M. Myers, MD, 48 W. Commercial St., Willits, CA 95490. Office: (707) 459-2765, Home: (707) 459-2938.

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FAMILY PRACTICE: Small, semi-rural Sonoma County Community, 50 minutes north of San Francisco, busy solo practice, 6 MD's share call, young practice (75 percent under age 40), teaching/education opportunities nearby. Contact Leigh Hall, MD, 707-938-0575, Drawer A, Glen Ellen, CA 95442.

FAMILY PRACTICE—Sacramento Valley quality practice in University town with ideal family environment. Medical school CME and excellent family practice oriented hospital within community. Available due to July residency. Negotiable terms. Evenings 916-756-4703 or reply Box 6038, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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INFORMATION

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EX 220

CONTINUING MEDICAL EDUCATION

California, Hawaii • Oregon • Washington • Montana, Alaska, Idaho

CALIFORNIA and HAWAII

This listing of continuing education programs in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

April 20-22—**Newer Concepts and Older Practices in Obstetrical Anesthesia.** Fresno Community Hospital. Friday-Sunday. Contact: Joanne Ellis, Fresno Community Hosp., P.O. Box 1232, Fresno 93715. (209) 442-6000, ext. 5696.

April 30-May 4—**California Society of Anesthesiologists—Hawaii Seminar.** Kauai Surf Hotel, Kauai. Monday-Friday. 20 hrs. Contact: CSA, Inc., 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

May 6-12—**16th Biennial Western Conference on Anesthesiology.** Sheraton Waikiki, Honolulu. One week. Contact: BWCA, 707-2525 Willow St., Vancouver, B.C., Canada V5Z 3N8.

May 31-June 4—**California Society of Anesthesiologists—Annual Scientific Meeting.** Disneyland Hotel, Anaheim. Thursday-Monday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

June 22-24—**Practical Closed System Anesthesia.** PMC. Friday-Sunday.

August 4—**Obstetrical Anesthesia.** Mercy Hospital and Medical Center, San Diego. Saturday. Contact: Gilbert E. Kinyon, MD, Dir. of Anesthesia, Mercy Hospital & Medical Center, 4077 Fifth Ave., San Diego 92103. (714) 294-8037.

CANCER

May 19—**Problems, Therapies and Complications in Cancer—Genital, Urinary and Colo-Rectal.** San Francisco Regional Cancer Foundation at Fireman's Fund Building, San Francisco. Saturday. 4 hrs. Contact: Terry Sheehy, PhD, S.F. Regional Cancer Fnd., 14th and Lake, San Francisco 94118. (415) 221-2132.

June 18-22—**Head and Neck Oncology.** UCLA. Monday-Friday. 35 hrs. $400.

July 13-14—**Oncology Symposium.** Area Health Education Center, UCSF, at Del Monte Hyatt, Monterey. Friday-Saturday. Contact: Remi Barron, Area Health Education Ctr., P.O. Box 1611, Salinas 93902. (408) 757-3616.

September 20-22—**Bladder Cancer.** American Urological Assn. at Hilton Hotel, San Diego. Thursday-Saturday. 16 hrs. $200, members; $250, nonmembers. Contact: Mary Rohan, AUA Office of Education, P.O. Box 1129, Aspen, CO 81611. (303) 925-2012.

September 26—**Head and Neck Cancer Symposium.** Hospital of the Good Samaritan, Los Angeles. Wednesday. 7 hrs. Contact: Janie Sternal, CME Coordinator, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

EMERGENCY MEDICINE

April 21-28—**Emergency Medicine.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 29 hrs. $325.

April 30—**Polyneuropathies.** General Hospital Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at General Hospital, Ventura. Monday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

May 7-11—**Topics in Emergency Medicine.** UCSF at Sheraton, Fisherman's Wharf, San Francisco. Monday-Friday.

May 9—**Symposium on Emergency Medicine.** N. T. Enloe Memorial Hospital at Holiday Inn, Chico. Wednesday. 7 hrs. $35. Contact: Mr. C. H. Weagle, Asst. Admin., N. T. Enloe Memorial Hosp., 5th Ave. & Esplanade, Chico. (916) 342-1841, ext. 296.

May 14-18—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Islandia Hyatt House, San Diego. Monday-Friday. 40 hrs. $350.

May 19—**Emergency Radiology.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7½ hrs. $50.

May 21—**Hand Injuries.** General Hospital Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at General Hospital, Ventura. Monday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

June 6-10—**Seminar in the Sierra: Postgraduate Course in Emergency Medicine.** Doctor's Essential Services, Inc., and Providence Hosp., Oakland, at Stanford Sierra Lodge, Fallen Leaf Lake, Lake Tahoe. Wednesday-Sunday. 21 hrs. $195. Contact: D. Craig Dennis, MD, 897 MacArthur Blvd., San Leandro 94577. (415) 632-1504.

June 20-22—**Symposium on Emergency Room Radiology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Thursday. 16 hrs. $160.

June 25-29—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

August 13-17—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 43 hrs. $350.

September 24-28—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday. 43 hrs. $350.

MEDICINE

April 18—**Thyroid '79.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. $50. Contact: Janie Sternal, CME Coordinator, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

April 18—**Society of Nuclear Medicine, Southern California Chapter.** See Radiology and Pathology, April 18.

April 26-June 14—**Current Practical Cardiology—1979.** Daniel Freeman Hospital, Inglewood. Thursdays; 6:30-9:00 p.m. 16 hrs. $120. Contact: Donald A. Dennis, PhD, Dir. of Med. Ed., 333 N. Prairie, Inglewood 90301. (213) 674-7050, ext. 3427.

April 27—**Controversies in Cardiology.** American Heart Assn., Santa Clara County Chapter, at Le Baron Hotel, San Jose. Friday. 6 hrs. $30. Contact: Harriet M. Schutte, RN, PhD, AHA, Santa Clara Co. Chap., 3003 Moorpark Ave., San Jose 95128.

May 3-5—**Critical Care Cardiology.** PMC. Thursday-Saturday. 18 hrs.

May 4-5—**Selected Aspects of Clinical Neuroendocrinology.** Cedars-Sinai Medical Center, Los Angeles. Friday-Saturday. $75. Contact: Lore Kahane, Rm. 2049, Cedars-Sinai Med. Ctr., Box 48750, Los Angeles 90048.

May 4-6—**Sierra Valley Nuclear Medicine Association.** See Radiology and Pathology, May 4-6.

May 4-6—**Coronary Disease, Exercise Testing and Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton Inn, San Diego. Friday-Sunday. 13 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

May 5—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

May 6-11—**Internal Medicine for the Primary Care Physician.** UCD at Hilton Riviera, Palm Springs. Sunday-Friday. 42½ hrs. $275.

May 11-13—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Sheraton at the Wharf, San Francisco. Friday-Sunday. 15 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

May 12—**Controversies in Internal Medicine—3rd Annual Program.** San Jose Health Center at Marriott's Great America, Santa Clara. Saturday. 6 hrs. $40. Contact: Stanley Skillicorn, MD, Dir. of Med. Ed., San Jose Health Ctr., 675 E. Santa Clara, San Jose 95112. (408) 998-3212.

May 12-13—**Management of Thrombo-Embolic Disease in Clinical Practice.** UCLA. Saturday-Sunday. 14 hrs.

May 19-20—**Kidney Disease—19th Annual Symposium.** Kidney Foundation of So. Calif. at South Coast Plaza Hotel, Costa Mesa. Saturday-Sunday. Contact: Kidney Foundation of So. Calif., 1281 Westwood Blvd., Suite 200, Los Angeles 90024. (213) 473-6559.

May 23—**Diabetes Symposium.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Janie Sternal, CME Coordinator, 616 Witmer St., Los Angeles 90017. (213) 488-8123.

June 1-3—**Infectious Disease.** Area Health Education Ctr., UCSF, at Del Monte Hyatt, Monterey. Friday-Sunday. Contact: Remi Barron, Area Health Ed. Ctr., P.O. Box 1611, Salinas 93902. (408) 757-3616.

June 4-8—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

June 6—**Common Cardiovascular Problems in Children: An Update for the Practitioner.** American Heart Assn., Greater Los Angeles Affiliate, and Los Angeles Pediatric Soc. at Hilton Hotel, Los Angeles. Wednesday. 7 hrs. $40, AHA or LAPS members; $50, nonmembers. Contact: Jana Rogers, AHA, Greater LA Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

June 9-10—**Practical Cardiology for the Primary Care Physician.** UCLA. Saturday-Sunday.

June 13-16—**Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Wednesday-Saturday. Contact: Mary Anne McInerny, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 15-16—**Pheresis.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday.

June 20-22—**Pediatric Gastroenterology.** See Pediatrics, June 20-22.

June 27-29—**Hepatobiliary Disease in Clinical Practice.** PMC at Holiday Inn on Union Square, San Francisco. Wednesday-Friday. 15 hrs. $180.

July 13-15—**Cardiac Symptoms, Arrhythmias and Holter Monitoring.** International Medical Education Corp. at Hyatt, Anaheim. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

July 19-20—**New Approaches to Immunosuppression.** PMC at Fairmont Hotel, San Francisco. Thursday-Friday. 12 hrs. $100.

July 23-24—**Microcirculatory Approach to Current Medical and Surgical Problems.** Microcirculatory Society and American Heart Assn., Greater Los Angeles Affiliate, at Hilton, San Diego. Monday-Tuesday. 14 hrs. $175, before April 1; $200, thereafter. Contact: Nomi Feldman, Conf. Coordinator, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

July 27-29—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Sunday. 15 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

July 30-August 3—**Endocrinology and Metabolism.** UCSF at Hyatt Regency, San Francisco. Monday-Friday.

August 4—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

September 16-20—**Pacific Dermatologic Association—Annual Meeting.** Hyatt Regency, San Francisco. Sunday-Thursday. 15½ hrs. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno NV 89509. (702) 323-2461.

September 24-28—**An Advanced Course for Internists.** STAN at San Francisco. Monday-Friday.

September 28-30—**Coronary Disease, Exercise Testing and Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton on the Wharf, San Francisco. Friday-Sunday. 13 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

OBSTETRICS AND GYNECOLOGY

April 15-21—**Current Dialogues in Obstetrics and Gynecology.** Memorial Hospital Medical Center of Long Beach and

Women's Hospital of Long Beach at Kauai Surf, Kalapaki Beach, Hawaii. One week. 22 hrs. $300. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 9—**Hormones and Hormone Therapy.** LLU. Wednesday. 4 hrs.

May 21-23—**Recent Advances in Obstetrics and Gynecology.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 18 hrs. $250.

August 25-31—**Edward Tyler Symposium on the Practical Management of the Infertile Couple—3rd Annual.** Tyler Medical Clinic, Los Angeles, and Univ. of Hawaii School of Medicine at Maui Surf Hotel, Maui, Hawaii. One week. 16 hrs. $200. Contact: Jetset Tours, 2029 Century Park East, Suite 2130, Los Angeles 90067.

PEDIATRICS

May 5—**Pediatric Dermatology Seminar.** See Medicine, May 5.

May 7-11—**Pediatric Review—9th Annual.** USC. Monday-Friday.

May 9-11—**Care of the Sick Newborn.** Memorial Hospital Medical Center, Long Beach. Wednesday-Friday. 18 hrs. $125. Contact: Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

May 10-12—**Annual Pediatric Course.** UCSF at Golden Gateway Holiday Inn, San Francisco. Thursday-Saturday.

May 12-19—**Pediatric Workshop.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 28 hrs. $325.

May 26-28—**Practical Problems in Pediatrics.** American Academy of Pediatrics, No. Calif. Chapter 1, at Del Monte Hyatt, Monterey. Saturday-Monday. $100, members; $125, nonmembers. Contact: Karen Brown, 604 Fortress Isle, Alameda 94501. (415) 523-3760.

June 6—**Common Cardiovascular Problems in Children: An Update for the Practitioner.** See Medicine, June 6.

June 16—**Update of Pediatric Ophthalmology.** See Surgery, June 16.

June 20-22—**Pediatric Gastroenterology.** UCSF. Wednesday-Friday.

August 4—**Pediatric Dermatology Seminar.** See Medicine, August 4.

PSYCHIATRY

April 24—**Continuing Medical Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

April 28—**Dance/Movement Therapy: The Window to Analogic Communication.** Mental Research Institute, Palo Alto. Saturday. $50. Contact MRI, 555 Middlefield Rd., Palo Alto 94301.

May 19—**Community Treatment of Schizophrenia.** Mental Research Institute, Palo Alto. Saturday. $60. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

May 29—**Continuing Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

June 1-2—**Psychosocial Care of the Dying Patient.** UCSF. Friday-Saturday.

June 1-3—**Infant Psychiatry II.** UCSF. Friday-Sunday.

June 8-10—**Family Therapy—Approaches and Techniques.** Cedars-Sinai Med. Ctr., Thalians Community Mental Health Ctr., and So. Calif. Psychiatric Soc. at Beverly Hilton, Beverly Hills. Friday-Monday. 15½ hrs. Contact: Ellen G. Ruderman, LCSW, Thalians Community Memorial Health Ctr., 8730 Alden Dr., Los Angeles 90048. (213) 855-3403.

June 13—**Diagnosis and Office Management of Anxiety and Stress.** LLU. Wednesday. 4 hrs.

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June 16-23—**Comparative Psychotherapies.** USC at Royal Lahaina, Maui, Hawaii. One week. 26¾ hrs. $300.

September 15—**Psychopharmacology in Clinical Practice: A Practicum in Mind-Allergy Drugs.** UCLA. Saturday.

RADIOLOGY AND PATHOLOGY

April 18—**Society of Nuclear Medicine, Southern California Chapter—Annual Benedict Cassen Memorial Lecture Dinner Meeting.** L.A. Co. Med. Assn. Headquarters, Los Angeles. Wednesday. Contact: Jean Lynch, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

April 19-20—**Radiology Seminar—Clinical Problems.** UCSF. Thursday-Friday.

May 3-4—**Radiology Seminar—Clinical Problems.** UCSF. Thursday-Friday.

May 4-6—**Sierra Valley Nuclear Medicine Association—11th Annual Spring Symposium.** Northern Calif. Chapter, Society of Nuclear Medicine, at MGM Grand Hotel, Reno. Friday-Sunday. Contact: Cathy Suey, Nuclear Medicine, 4301 X St., Sacramento 95817.

May 11-13—**Radiology of the Pneumoconioses.** American College of Radiology at San Francisco. Friday-Sunday. 15 hrs. Contact: ACR, 6900 Wisconsin Ave., Chevy Chase, MD 20015.

May 19—**Emergency Radiology.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7½ hrs. $50.

May 19-20—**Pathology of the Endocrine System.** UCLA at Long Beach Convention Center. Saturday-Sunday.

June 14-15—**Modern Gastrointestinal Radiologic Techniques for the Practicing Physician.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Friday. 13 hrs. $200.

June 17-22—**Pathology of the Lung.** UCSD at Summer House Inn, La Jolla. Sunday-Friday. 50 hrs. $450.

June 20-22—**Symposium on Emergency Room Radiology.** See Emergency Medicine, June 20-22.

July 28-August 4—**Medical Imaging.** American College of Medical Imaging at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

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SURGERY

April 18-20—**Vitrectomy.** UCSF. Wednesday-Friday.

April 19-20—**Neuro-Ophthalmology—10th Annual Jules Stein Lecture and Postgraduate Seminar.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. Thursday-Friday. 16 hrs. $225. Contact: Lu Hendricks, Academic Prog. Admin., Jules Stein Eye Inst., UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

April 19-21—**Wound Management Workshop.** UCSD, Div. of Plastic Surgery, at Islandia Hyatt House, San Diego. Thursday-Saturday.

April 19-21—**Advances in Clinical Neurourology.** American Urological Assn. at Hyatt Regency, San Francisco. Thursday-Saturday. 16 hrs. $200, members; $250, nonmembers. Contact: Jean Greiner, AUA Office of Education, P.O. Box 1129, Aspen, CO 81611. (303) 925-2012.

April 27-29—**Surgical Update.** UCD at Hyatt Lake Tahoe, Incline Village. Friday-Sunday. 9¼ hrs.

April 29-May 11—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Antonio De La Cruz, MD, Course Dir., ERI, 256 S. Lake St., Los Angeles 90057.

May 1-4—**24th Annual Samuel Higby Camp Lectureship and 14th Annual Scientific Program of the Leroy C. Abbott Orthopaedic Society.** UCSF. Tuesday-Friday. 14 hrs. Contact: Jana S. Smith, Alumni Sec., Univ. of Calif., Rm. U471, San Francisco 94143. (415) 666-1166.

May 10-11—**Surface Replacement.** UCLA. Thursday-Friday.

May 17-18—**Office Orthopedics.** USC. Thursday-Friday.

May 26—**Retinal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Jules Stein Eye Inst., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

May 31-June 1—**Neurosurgery—9th Annual Postgraduate Course.** UCSF at Hilton Hotel, San Francisco. Thursday-Friday.

June 3-15—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Antonio De La Cruz, MD, Course Dir., ERI, 256 S. Lake St., Los Angeles 90057.

June 14-16—**Highlights of Ophthalmology.** PMC. Thursday-Saturday. 15 hrs.

June 16—**Update of Pediatric Ophthalmolofy.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $75. Contact: Mrs. Lu Hendricks, Jules Stein Eye Inst., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

July 23-24—**Microcirculatory Approach to Current Medical and Surgical Problems.** See Medicine, July 23-24.

August 4-11—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 28 hrs. $325.

OF INTEREST TO ALL PHYSICIANS

April 19-21—**San Joaquin Valley Counties Postgraduate Institute.** CMA and UCSD at Ahwahnee Hotel, Yosemite. Thursday-Saturday. 14 hrs. $60, members; $90, nonmembers. Contact: Charlotte Newhart, CMA.

April 21—**Diagnostic Imaging for Primary Care Physicians.** PMC. Saturday. 6 hrs. $65.

April 21-22—**How Primary Care Physicians Can Enhance Their Patients' Health.** UCLA. Saturday-Sunday.

April 23-25—**The Body Fluids in Health and Disease.** UCSF. Monday-Wednesday.

April 26-27—**Youth Perspectives: Smoking and Health.** National and California Interagency Councils on Smoking and Health; and Center for Disease Control at Hilton Hotel, San Francisco. Thursday-Friday. $20. Contact: Calif. Interagency Council on Smoking and Health, 731 Market St., Suite 400, San Francisco 94103. (415) 777-1800.

April 28-May 5—**Diagnostic and Therapeutic Skills.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $325.

April 29-May 3—**American Occupational Medical Association—Annual Meeting.** Disneyland Hotel, Anaheim. Sunday-Thursday. 16½ hrs. $45, members; $65 nonmembers. Contact: Howard N. Schulz, Exec. Dir., AOMA, 150 N. Wacker Dr., Chicago 60606. (312) 782-2166.

May 4-5—**Providence Hospital Annual Spring Seminar.** Oakland. Friday-Saturday. Contact: Nancy Hansen, Coordinator, Med. Staff Services, Providence Hospital, 3012 Summit St., Oakland 94623. (415) 835-4500, ext. 373.

May 6-11—**Internal Medicine for the Primary Care Physician.** See Medicine, May 6-11.

May 15-21—**Diving Medicine, Basic.** UCSF at VA Hospital, Fresno. One week.

May 18-19—**UCSF—Alumni Day Program.** Friday-Saturday.

May 19-20—**Basic Skills in Sexual Counseling.** UCLA. Saturday-Sunday.

May 20-25—**Fingers-to-the-Toes: An Orthopedic Approach for the Family Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf. Sunday-Friday. 42½ hrs. $280.

May 21-25—**Orthopedics for the Primary Care Physician.** Bone and Joint Disease Foundation at Islandia Hyatt, Mission Bay, San Diego. Monday-Friday. Contact: Pat Curl, 5919 Caminito Yucatan, San Diego 92108. (714) 294-5944.

May 25-26—**Tropical Disease in the U.S.—Current Views on Diagnosis, Treatment and Epidemiology.** UCSF. Friday-Saturday.

June 1-2—**Psychosocial Care of the Dying Patient.** See Psychiatry, June 1-2.

June 2-3—**Family Practice Symposium—7th Annual.** So. Calif. Permanente Medical Group at Marriott Hotel, Newport Beach. Saturday-Sunday. Contact: Shirley Gach, SCPMG, Education & Research Dept., 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4516.

June 2-3—**Realistic Treatment for the Management of the Obese Patient.** UCLA. Saturday-Sunday. 13 hrs. $145.

June 7-9—**Metabolic and Nutritional Care of the Hospitalized Patient.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Saturday.

June 7-9—**Common Problems in Primary Care.** PMC at Stanford Court, San Francisco. Thursday-Saturday.

June 8-9—**Management of Medical Problems.** PMC. Friday-Saturday. 15 hrs.

June 11-16—**Family Practice Refresher Course.** UCI at South Coast Plaza Hotel, Costa Mesa. One week. 46 hrs. $290.

June 11-16—**Family Practice Review Course—6th Annual.** UCLA and Santa Monica Hospital Medical Center at Biltmore Hotel, Los Angeles. Monday-Saturday. 40 hrs. $300. Contact: UCLA.

June 18-22—**Family Practice Symposium.** UCSD at Islandia Hyatt, San Diego. Monday-Friday.

June 23-30—**Manipulative Medicine.** USC at Sheraton-Waikiki, Hawaii. One week. $325.

July 19-21—**Tissue Fluid Pressure and Composition.** UCSD. Thursday-Saturday. 17 hrs. $190.

August 4-11—**Hypnosis and Imagery: Practical Applications.** Bay General Community Hosp., Chula Vista, at Hotel Intercontinental, Maui, Hawaii. One week. 15 hrs. $150. Contact: Errol R. Korn, MD, 480 4th Ave., Suite 409, Chula Vista 92010. (714) 420-8051.

August 11-22—**Postgraduate Refresher Course—22nd Annual.** USC at Honolulu and Maui or Kauai, Hawaii. Two weeks. 39 hrs. $325.

August 19-25—**Family Practice Refresher Course—7th Annual.** UCD at Del Monte Hyatt, Monterey. One week. 30 hrs. $225.

August 25-31—**Edward Tyler Symposium on the Practical Management of the Infertile Couple—3rd Annual.** See Obstetrics and Gynecology, August 25-31.

September 9-13—**American Academy for Cerebral Palsy and Developmental Medicine—Annual Meeting.** St. Francis Hotel, San Francisco. Sunday-Thursday. 26 hrs. $95. Contact: Helen Bryan, Assoc. Exec. Dir., 1255 New Hampshire Ave. NW, #1030, Washington, DC 20036. (202) 659-8251.

September 15—**Psychopharmacology in Clinical Practice: A Practicum in Mind-Allergy Drugs.** See Psychiatry, September 15.

September 20—**California Venereal Disease Controllers' Clinical Session.** CMA Task Force on Venereal Disease, Calif. VD Controllers Assn. and Calif. Academy of Preventive Medicine at San Mateo. Thursday. Contact: Karin McGhee, CMA.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

OREGON

COUNCIL ON MEDICAL EDUCATION

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, 97213.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

May 2-6—**Oregon Academy of Family Physicians Annual Meeting.** Valley River Inn, Eugene. Contact: Skippie Patterson, Oregon Academy of Family Physicians, 2153 SW Main, Portland 97205.

INTERNAL MEDICINE

May 17-19—**Oregon Society of Internal Medicine/American College of Physicians Annual Meeting.** Jantzen Beach Red Lion, Portland. Contact: Joyce Gullixson, Oregon Society of Internal Medicine, 5210 SW Corbett Avenue, Portland 97201.

PEDIATRICS

May 10-12—**Oregon Pediatric Society Annual Meeting.** Red Lion Downtown, Portland. Contact: Edward L. Hendricks, MD, 12270 SW First St., Beaverton 97005.

OF INTEREST TO ALL PHYSICIANS

Circuit Course Programs—Contact: Joyce Gullixson, Oregon Medical Association, 5210 SW Corbett Avenue, Portland 97201.

May 2 (Medford)—**Child and Adolescent Psychiatric Problems.** Providence Hospital, 1:30 p.m.

May 10 (Pendleton)—**Dizziness/Syncope and Loss of Consciousness.** St. Anthony Hospital, 1:00 p.m.

May 17 (Albany)—**Pediatrics.** Albany General Hospital, 1:30 p.m.

May 17 (Lincoln City)—**Urology.** North Lincoln Hospital, 1:30 p.m.

May 23 (Salem)—**To Be Announced.** Salem Hospital, 1:30 p.m.

May 23 (Grants Pass)—**Medical Genetics.** Josephine General Hospital, 1:30 p.m.

May 24 (Klamath Falls)—**Medical Genetics.** Presbyterian Intercommunity Hospital, 1:30 p.m.

May 30 (Astoria)—**Office Psychiatric Problems.** Columbia Memorial Hospital, 1:30 p.m.

May 30 (Ontario)—**Office Gynecology.** Holy Rosary Hospital, 1:30 p.m.

May 31 (Bend)—**Dizziness/Syncope and Loss of Consciousness.** St. Charles Hospital, 1:30 p.m.

April 19-20—**Dermatology for the Non-Dermatologist.** Red Lion, Jantzen Beach, Portland. Contact: J. S. Reinschmidt, MD, Dept. of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

April 26-27—**Oregon Heart Association Annual Scientific Session.** Red Lion, Portland Center, Portland. Contact: Audrey Booth, Oregon Heart Association, 1500 SW 12th Avenue, Portland 97201.

June 4-6—**Update: Emergency Medicine.** Salishan Lodge, Gleneden Beach. Contact: Richard A. Tuscher, DO, 2900 SE Steele St., Portland 97202.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

April 17—**Intrauterine Growth and Retardation—Univ. of Wash. OB-GYN Sessions** (Spokane). Tuesday, 12-1 p.m. Sacred Heart Medical Center. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

April 20-22—**Advanced Cardiac Life Support, Providers Course.** Seattle, Friday 6-9 p.m.—Saturday—Sunday. North Seattle Community College. Contact: Ron Rutherford, Course Coordinator, North Seattle Community College, 9600 College Way North, Seattle WA 98103. (206) 634-4482.

April 21—**Wenatchee Valley Clinic Day.** Wenatchee, Saturday. Wenatchee Valley Medical Clinic. 7 prescribed hrs. Contact: Gerald E. Gibbons, MD, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

April 23-24—**Drug Interactions—Univ. of Wash. Internal Medicine Review Sessions.**

April 23—Monday, Wenatchee. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, Wenatchee Valley Clinic, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

April 24, Tuesday, Yakima. 5-7 p.m., Memorial Hospital. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

April 26—**Management of Hypertension.** Seattle, Thursday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

April 28—**Medicine—Tacoma General Hospital Day.** Tacoma, Wednesday. Tacoma General Hospital. Contact: Maxine Bailey, College of Medical Education, 1500 North Warner, Tacoma, WA 98416. (206) 756-3152.

May 3-4—**Medical Alumni Days—Controversies in Medicine.** Seattle, Thursday-Friday. Contact U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 4-5—**Medical Applications of Real Time Ultrasound.** Seattle, Friday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 7-8 **Management of Birth Defects.** Seattle, Monday-Tuesday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

May 11—**Participation Seminar: Management of Cirrhosis of the Liver.** Seattle, Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

May 11-12—**Annual Scientific Assembly—Washington Academy of Family Physicians.** Spokane, Friday-Saturday. Red Lion Motor Inn. 14 prescribed hours. Contact: Carolyn M. Palmer, Washington Academy of Family Physicians, 3700 140th Ave, NE, Bellevue, WA 98005. (206) 883-8852.

May 14-15—**Immunoglobulins and Immunologic Disease—Univ. of Wash. Internal Medicine Review Sessions.**

May 14, Monday, Wenatchee. 7:30-9:30 p.m. Wenatchee Valley Clinic. Contact: William McKee, MD, Wenatchee Valley Clinic, P.O. Box 489, Wenatchee, WA 98801. (509) 663-8711.

May 15, Tuesday, Yakima. 5-7 p.m., Memorial Hospital. Contact: Harry R. Kimball, MD, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

May 15—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Spokane). Tuesday, 12-1 p.m., Sacred Heart Medical Center, Spokane. Contact: Frank Reynolds, MD, WAMI Office, 3 North, Sacred Heart Medical Center, Spokane, WA 99204. (509) 455-8220.

May 19—**Upper Extremity Orthopedics in Primary Care.** Seattle, Saturday. Group Health Cooperative of Puget Sound. Contact: Office of Education, Group Health, A-5, 201 16th Avenue E., Seattle, WA 98112. (206) 326-7348.

May 19-20—**Extracapsular Cataract Surgery and Artificial Lens Implantation: The Northwest Course.** Bellevue, Saturday-Sunday. Overlake Hospital. Contact: David J. McIntyre, MD, Northwest Microsurgical Institute, Inc., 1035 116th Ave., NE, Bellevue, WA 98004. (206) 454-7912.

May 22—**Gynecologic Cancer—Univ. of Wash. OB-GYN Sessions** (Spokane). Tuesday, 12-1 p.m., Sacred Heart Medical Center, Spokane. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 31 and June 1—**Respiratory Care.** Seattle, Thursday-Friday. Contact U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 1—**Management of Acute Surgical Problems.** Seattle, Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 2-3—**Colon and Rectal Surgery.** Seattle, Saturday-Sunday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 7-8—**Surgery.** Seattle, Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 21-23—**American College of Cardiology: Medical and Surgical Management of Coronary Artery Disease.** Seattle, Thursday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 23-24—**The American Medical Heritage: Hematic, Heroic and Heretical.** Sun Valley, Idaho, Saturday-Sunday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 25-26—**Platelets and Clotting—Univ. of Wash. Internal Medicine Review Sessions.**

June 25—Monday, Wenatchee. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, Wenatchee Valley Clinic, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

June 26, Tuesday, Yakima. 5-7 p.m., Memorial Hospital. Contact: Harry Kimball, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

August 16-18—**Controversies in Otolaryngology.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

ALASKA, MONTANA AND IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

April 25—**Gynecologic Oncology—Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

May 10—**Consultation With the Alaskan Native Child—Univ. of Wash. Psychiatry Sessions** (Anchorage). Thursday. Contact: Robert F. Kraus, MD, Star Route A, Box 26-B, Anchorage, AK 99507. (907) 344-7863.

May 11-12—**Fifth Alaska Health Congress**—Anchorage, Friday-Saturday. International Roadway Inn. Contact: Arnie Beltz, Anchorage Health Department, 825 L St., Anchorage, AK 99501. (907) 246-4607.

June 6-8—**Alaska State Medical Association Annual Meeting**—Sitka, Wednesday-Friday. Shee Atika Lodge. Contact: Alaska State Medical Association, 1135 W. 8th Ave., Suite 6, Anchorage, AK 99501. (907) 277-6891.

June 27—**Diabetes in Pregnancy—Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

MONTANA

April 20-21—**Advanced Cardiac Life Support and Critical Care for Physicians and Nurses.** Kalispell, Friday-Saturday. Outlaw Inn. Contact: Jack L. Davis, MD, 210 Sunnyview Lane, Kalispell, MT 59901. (406) 755-7406.

April 25-27—**Coronary Artery Disease: Medical and Surgical Therapy—Univ. of Wash. Internal Medicine Review Sessions.**

April 25, Wednesday, Great Falls. 4:30-7:30 p.m., Columbus Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

April 26, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

April 27, Friday, Missoula. 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

May 4-5—**Montana Heart Association Annual Postgraduate Conference for Physicians**—Great Falls, Friday-Saturday. Heritage Inn. Contact: John Connor, Exec. Dir., Montana Heart Association, 510 First Ave. N., Great Falls, MT 59401. (406) 452-2362.

May 16-17—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions.**

May 16, Wednesday, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 17, Thursday, Kalispell. 11:30 a.m.-1 p.m., Kalispell Hospital. Contact: Ronald Miller, MD, 4th and Baker, Whitefish, MT 59937. (406) 862-2515.

May 19—**Sports Medicine for Primary Physicians**—Missoula, Saturday. Western Montana Clinic. 7 hrs. Contact: A. G. Peterson, MD, Western Montana Clinic, 501 W. Broadway, Missoula, MT 59801. (406) 549-6181.

June 1-2—**Billings Clinic Foundation Medical Surgical Symposium**—Billings, Friday-Saturday. Northern Hotel. Contact: Paul Grmoljez, MD, P.O. Box 2555, Billings, MT 59103. (406) 252-4141.

June 6-8—**Acute Respiratory Failure and Health Effects of Asbestos—Univ. of Wash. Internal Medicine Review Sessions.**

June 6, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

June 7, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

June 8, Friday, Missoula. 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

June 21-23—**Montana Academy of Family Physicians' 29th Annual Scientific Assembly.** Fairmont Hot Springs. Thursday-Saturday. Contact: R. Bruce Beithon, MD, Twin Bridges, MT 59754. (406) 684-5642.

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: June 6-8, 1979, Shee Atika Lodge, Sitka.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 25-29, 1979, Safari Hotel, Scottsdale.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: March 9-12, 1979, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 19-23, 1979, the Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 8-12, 1979, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: June 20-23, 1979, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 4-6, 1979, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 18-20, 1979, Ely Convention Center, Ely.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 2-4, 1979, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Meeting of House of Delegates: April 20-22, 1979, Valley River Inn, Eugene. Annual Scientific Meeting: November 2-4, 1979, OMA Headquarters.

Utah State Medical Association—42 S. 5th East St., Salt Lake City 84102. Annual Meeting: September 11-14, 1979, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 4-7, 1979, Washington Plaza Hotel, Seattle.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: August 28-31, 1979, Jackson Lake Lodge, Moran.

August 9-11—**Montana/Wyoming Chapter, American College of Surgeons' Annual Meeting**—Big Sky. Thursday-Saturday. Meadow Village. Contact: Charles F. Rinker, MD, 300 N. Willson, Bozeman, MT 59715. (406) 587-0704.

September 7-8—**Montana/Wyoming Chapter, American College of Physicians' Regional Meeting**—Fairmont Hot Springs, Friday-Saturday. Contact: J. E. McGreevey, MD, 401 S. Alabama, Butte, MT 59701. (406) 723-4384.

IDAHO

April 16—**Intrauterine Growth and Retardation—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391.

April 17—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 S. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

April 27-28—**Idaho OB-GYN Society Meeting.** Boise, Friday-Saturday, Sheraton Downtown Inn. Contact: Gloria Stone, P.O. Box 2668, Boise, ID 83701. (208) 344-7888.

May 21—**Gynecologic Cancer—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital, Boise. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391.

May 22—**Pediatric Pathology: Role of the Laboratory in Pediatric Diagnosis—Test Selection and Interpretation—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 E. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

June 23-24—**The American Medical Heritage: Hematic, Heroic and Heretical**—Sun Valley. Saturday-Sunday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

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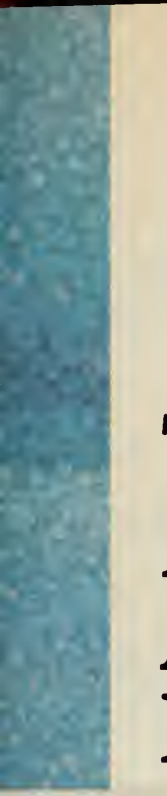
THE EMOTIONAL-NEURAL LINK IN DUODENAL ULCER*

How excessive anxiety may induce vagal stimulation of acid-pepsin secretion

A manifestation of emotional stress, excessive anxiety may induce gastric hypersecretion by its effect on central and peripheral neural activity. Hypothalamic mediation of *vagal* activity increases acid and pepsin output,[1,2] leading to exacerbation of the distressing symptoms of duodenal ulcer.

Artist's impression of peripheral nerve ramifying on the surface of gastric mucosal cells. Illustration based on a cross section of gastric wall as seen by scanning electron microscope.

1. Sun DCH: Etiology and pathology of peptic ulcer, chap. 27, vol. 1, in *Gastroenterology*, ed. 3, edited by Bockus HL, *et al*. Philadelphia, W.B. Saunders Company, 1974, pp. 586, 592-593. 2. Palmer ED: *Clinical Gastroenterology*, ed. 2. New York, Hoeber Medical Division, Harper & Row, Publishers, 1963, p. 202.



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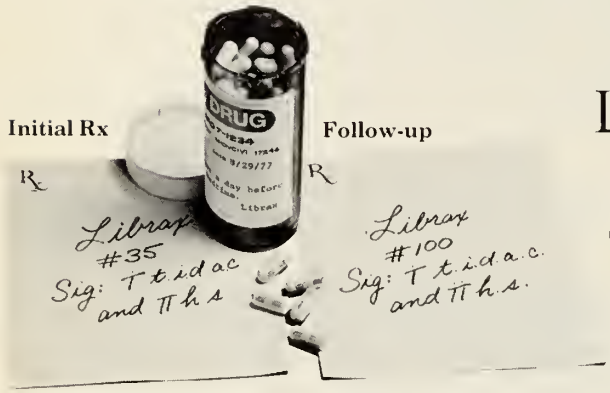

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"Possibly" effective: as adjunctive therapy in the treatment of peptic ulcer and in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Final classification of the less-than-effective indications requires further investigation.

Contraindications: Glaucoma; prostatic hypertrophy, benign bladder neck obstruction; hypersensitivity to chlordiazepoxide HCl and/or clidinium Br.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants, and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Physical and psychological dependence rarely reported on recommended doses, but use caution in administering Librium® (chlordiazepoxide HCl) to known addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions) reported following discontinuation of the drug.

***Usage in Pregnancy:* Use of minor tranquilizers during first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy. Advise patients to discuss therapy if they intend to or do become pregnant.**

As with all anticholinergics, inhibition of lactation may occur.

Precautions: In elderly and debilitated, limit dosage to smallest effective amount to preclude ataxia, oversedation, confusion (no more than 2 capsules/day initially; increase gradually as needed and tolerated). Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider pharmacology of agents, particularly potentiating drugs such as MAO inhibitors, phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions reported in psychiatric patients. Employ usual precautions in treating anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship not established.

Adverse Reactions: No side effects or manifestations not seen with either compound alone reported with Librax. When chlordiazepoxide HCl is used alone, drowsiness, ataxia, confusion may occur, especially in elderly and debilitated; avoidable in most cases by proper dosage adjustment, but also occasionally observed at lower dosage ranges. Syncope reported in a few instances. Also encountered: isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent, generally controlled with dosage reduction; changes in EEG patterns may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice, hepatic dysfunction reported occasionally with chlordiazepoxide HCl, making periodic blood counts and liver function tests advisable during protracted therapy. Adverse effects reported with Librax typical of anticholinergic agents, *i.e.*, dryness of mouth, blurring of vision, urinary hesitancy, constipation. Constipation has occurred most often when Librax therapy is combined with other spasmolytics and/or low residue diets.

Dosage: Individualize for maximum benefit. Usual maintenance dose is 1-2 capsules, 3-4 times/day, before meals and at bedtime. Geriatric patients—see Precautions.

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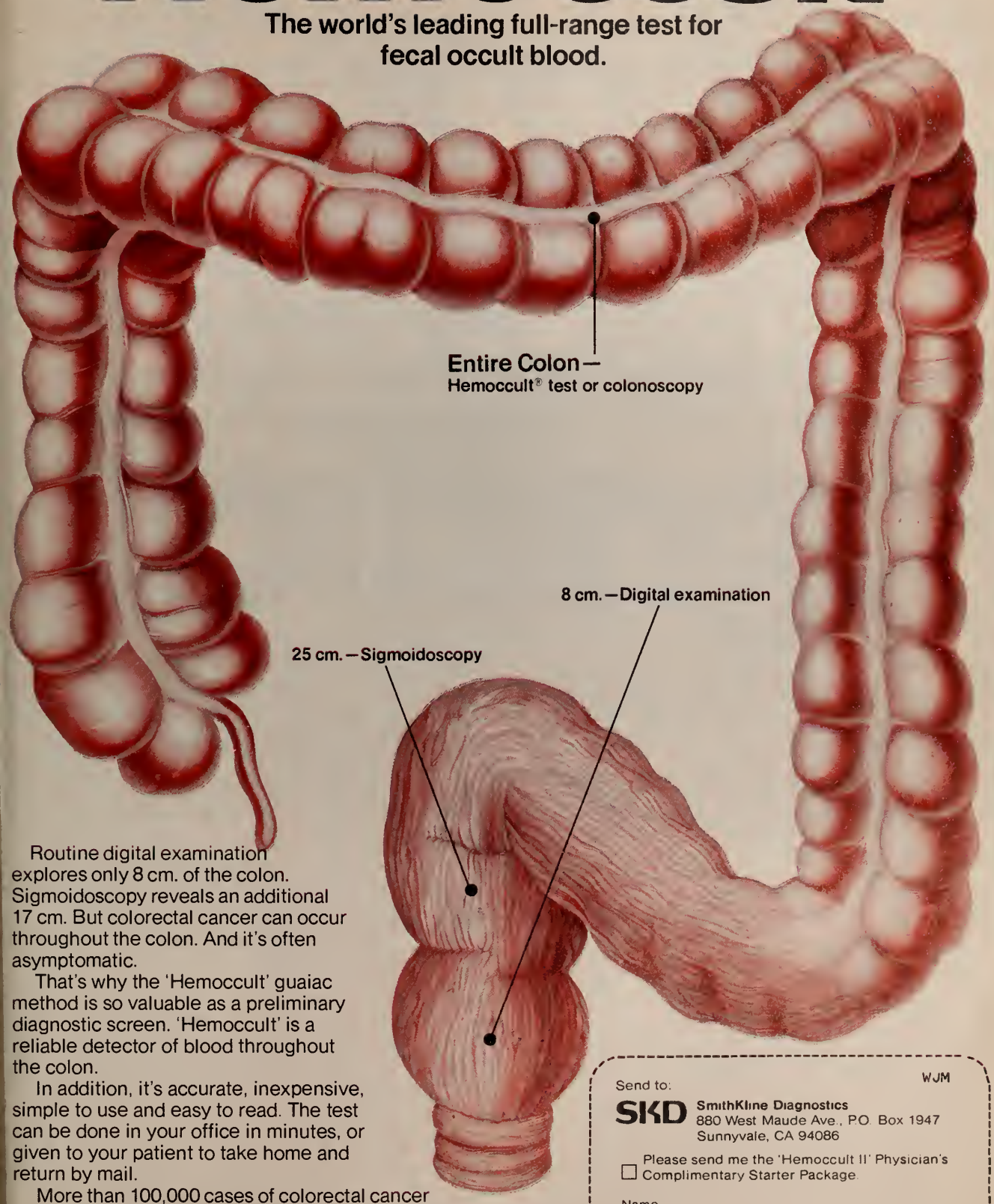

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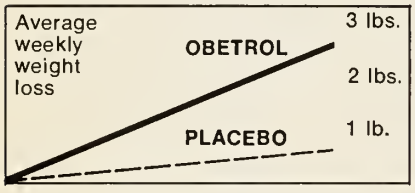

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Actions: Amphetamines are sympathomimetic amines with CNS stimulant activity. Peripheral actions include elevation of systolic and diastolic blood pressures and weak bronchodilator and respiratory stimulant action. The anorectic effect diminishes after a few weeks.

Indications: Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. For patients in whom obesity is refractory to other measures.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncracy to the sympathomimetic amines. • Agitated states. • Patients with a history of drug abuse. • During or within 14 days following the administration of monoamine oxidase inhibitors, hypertensive crises may result.

Warnings: Tolerance to the anorectic effect usually develops within a few weeks. When this occurs, the recommended dose should not be exceeded in an attempt to increase the effect, rather, the drug should be discontinued. Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle; the patient should therefore be cautioned accordingly.

Precautions: Caution is to be exercised in prescribing amphetamines for patients with even mild hypertension. Insulin requirements in diabetes mellitus may be altered in association with the use of amphetamines and the concomitant dietary regimen. Amphetamines may decrease the hypotensive effect of guanethidine. The least amount feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage.

Adverse Reactions: *Cardiovascular:* Palpitation, tachycardia, elevation of blood pressure. Central nervous system: Overstimulation, restlessness, dizziness, insomnia, euphoria, dysphoria, tremor, headache; rarely, psychotic episodes at recommended doses. *Gastrointestinal:* Dryness of the mouth, unpleasant taste, diarrhea, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. *Allergic:* Urticaria. *Endocrine:* Impotence, changes in libido.

Dosage and Administration: Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening medication should be avoided because of the resulting insomnia.

1. Narcolepsy: Usual dose 5 to 60 milligrams per day in divided doses.
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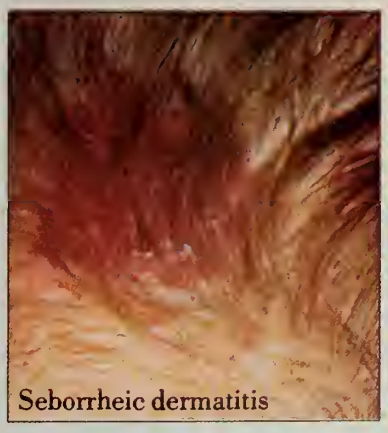
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PRECAUTIONS:
General—If irritation develops, discontinue the product and institute appropriate therapy. In presence of an infection, institute use of a suitable antibacterial or antifungal agent. If a favorable response does not occur promptly, discontinue the corticosteroid until the infection has been adequately controlled. If extensive areas are treated or if the occlusive technique is used, there will be increased systemic absorption of the corticosteroid and suitable precautions should be taken, particularly in children and infants. These preparations are not for ophthalmic use.
Usage in Pregnancy—Although topical steroids have not been reported to have an adverse effect on human pregnancy, the safety of their use in pregnant women has not been absolutely established. In laboratory animals, increases in incidence of fetal abnormalities have been associated with exposure of gestating females to topical corticosteroids—in some cases at rather low dosage levels. Therefore, drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.
Occlusive Dressing Technique—The use of occlusive dressing increases the percutaneous absorption of corticosteroids. For patients with extensive lesions it may be preferable to use a sequential approach, occluding one portion of the body at a time. Keep the patient under close observation if treated with the occlusive technique over large areas and over a considerable period of time. Occasionally, a patient who has been on prolonged therapy, especially occlusive therapy, may develop symptoms of steroid withdrawal when the medication is stopped. Thermal homeostasis may be impaired if large areas of the body are covered. Discontinue use of the occlusive dressing if elevation of the body temperature occurs.

Occasionally, a patient may develop a sensitivity reaction to a particular occlusive dressing material or adhesive and a substitute material may be necessary. If infection develops, discontinue the use of the occlusive dressing and institute appropriate antimicrobial therapy.

ADVERSE REACTIONS: The following local adverse reactions have been reported with topical corticosteroids, especially under occlusive dressings: burning sensations, itching, irritation, dryness, folliculitis, hypertrichosis, acneform eruptions, perioral dermatitis, allergic contact dermatitis, hypopigmentation, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

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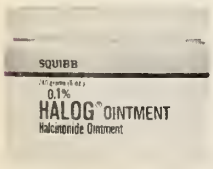
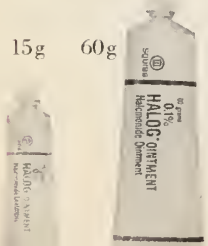
HOW SUPPLIED: The 0.025% and 0.1% Cream and the 0.1% Ointment are supplied in tubes of 15 g and 60 g, and in jars of 240 g (8 oz). The 0.1% Solution is supplied in plastic squeeze bottles of 20 ml and 60 ml.

Halog Ointment 0.1%
Halcinonide Ointment 0.1%

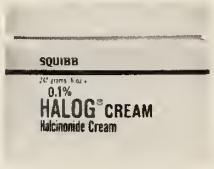


240 g

15 g 60 g



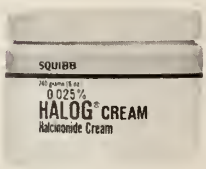
Halog Cream 0.1%
Halcinonide Cream 0.1%



240 g

15 g 60 g

Halog Cream 0.025%
Halcinonide Cream 0.025%



240 g

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Each tablet contains aspirin, 227 mg; phenacetin, 162 mg; and caffeine, 32 mg; plus codeine phosphate in one of the following strengths: #4—60 mg (gr 1); #3—30 mg (gr ½); #2—15 mg (gr ¼); and #1—7.5 mg (gr ⅛), (Warning—may be habit-forming). C III

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Vasodilan injection, isoxsuprine HCl, 5 mg., per ml.

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Intramuscular: 5 to 10 mg. (1 or 2 ml.) two or three times daily. Intramuscular administration may be used initially in severe or acute conditions.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Parenteral administration is not recommended in the presence of hypotension or tachycardia.

Intravenous administration should not be given because of increased likelihood of side effects.

Adverse Reactions: On rare occasions oral administration of the drug has been associated in time with the occurrence of hypotension, tachycardia, nausea, vomiting, dizziness, abdominal distress, and severe rash. If rash appears the drug should be discontinued.

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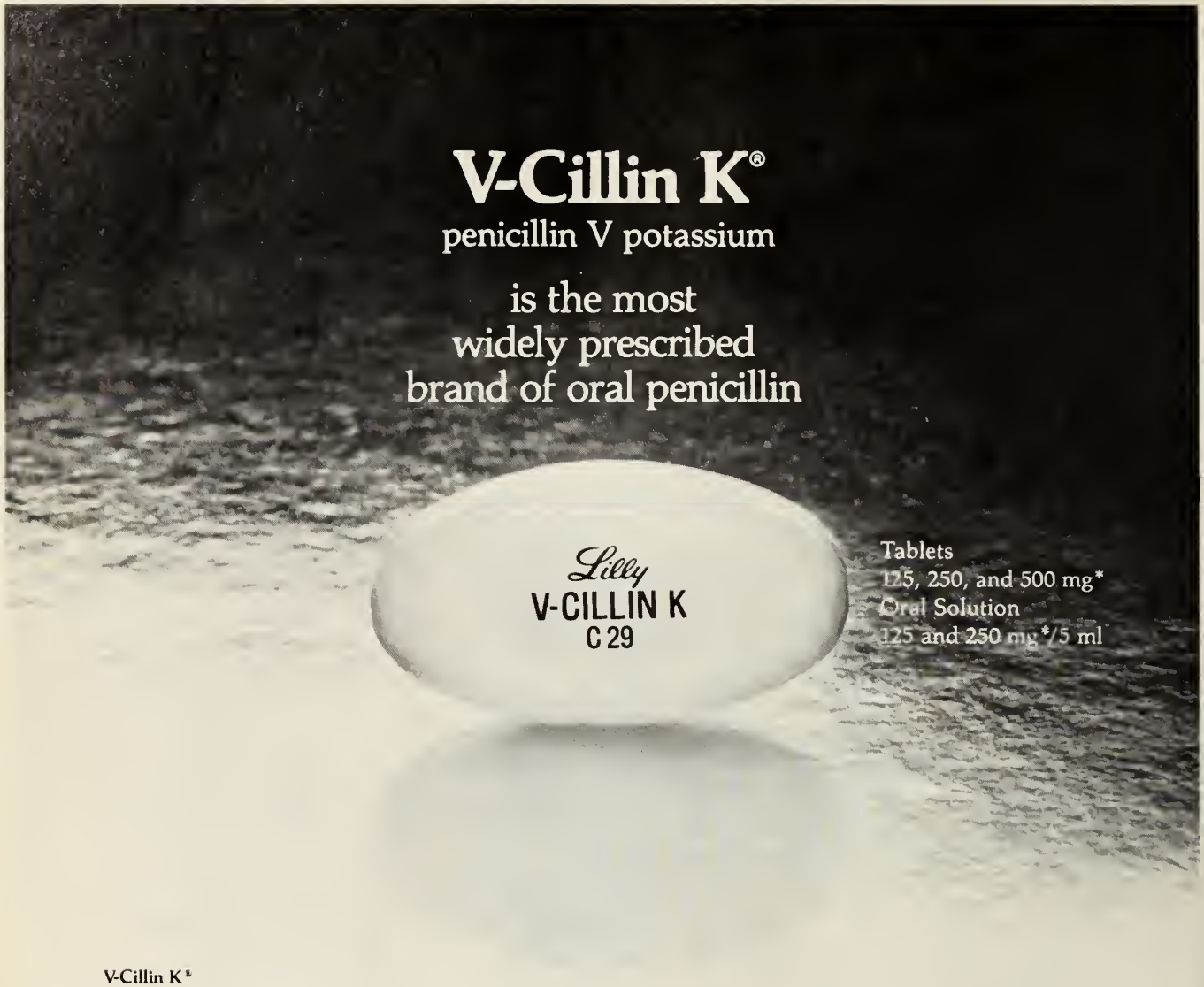

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Precautions: Use with caution in individuals with histories of significant allergies and/or asthma. Do not rely on oral administration in patients with severe illness, nausea, vomiting, gastric dilatation, cardiospasm, or intestinal hypermotility. Occasional patients will not absorb therapeutic amounts given orally. In streptococcal infections, treat until the organism is eliminated (minimum of ten days). With prolonged use, nonsusceptible organisms, including fungi, may overgrow; treat superinfection appropriately.

Adverse Reactions: Hypersensitivity, including fatal anaphylaxis. Nausea, vomiting, epigastric distress, diarrhea, and black, hairy tongue. Skin eruptions, urticaria, reactions resembling serum sickness (including chills, edema, arthralgia, prostration), laryngeal edema, fever, and eosinophilia. Infrequent hemolytic anemia, leukopenia, thrombocytopenia, neuropathy, and nephropathy, usually with high doses of parenteral penicillin. (102175)

***Equivalent to penicillin V.**

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In Edema* or Hypertension* when potassium balance is a concern...

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Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

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Serum K^+ and BUN should be checked periodically particularly in the elderly, diabetics, and those with suspected or confirmed renal insufficiency (see Warnings). If hyperkalemia develops, substitute a thiazide alone.

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in postsympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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See following page for brief summary

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Procainamide Hydrochloride Tablets

The prolonged administration of procainamide often leads to the development of a positive anti-nuclear antibody (ANA) test with or without symptoms of lupus erythematosus-like syndrome. If a positive ANA titer develops, the benefit/risk ratio related to continued procainamide therapy should be assessed. This may necessitate considerations of alternative anti-arrhythmic therapy.

DESCRIPTION: Pronestyl (Procainamide Hydrochloride) is the amide analogue of procaine hydrochloride and is available for oral administration as veneer-coated tablets providing 250 mg, 375 mg, and 500 mg procainamide hydrochloride.

CONTRAINDICATIONS: In patients with myasthenia gravis and where a hypersensitivity to procainamide exists; bear in mind cross sensitivity to procaine and related drugs. Should not be given to patients with complete atrioventricular heart block. Contraindicated in cases of second degree and third degree A-V block unless an electrical pacemaker is operative.

PRECAUTIONS: Evidence of untoward myocardial responses should be carefully watched for in all patients. In the presence of myocardial damage with atrial fibrillation or flutter, the ventricular rate may increase suddenly as the atrial rate is slowed; adequate digitalization reduces but does not abolish this danger. Ventricular tachysystole is particularly hazardous if myocardial damage exists.

The dislodgment of mural thrombi producing an embolic episode may occur in correcting atrial fibrillation due to the forceful contractions of the atrium.

Extreme caution is required in attempting to adjust the heart rate when ventricular tachycardia has occurred during an occlusive coronary episode or where the use of procainamide may result in additional depression of conduction and ventricular asystole or fibrillation as in second degree and third degree A-V block, bundle branch block, or severe digitalis intoxication.

Bear in mind when treating ventricular arrhythmias in patients with severe organic heart disease and ventricular tachycardia that complete heart block, which may be difficult to diagnose, may be present. Since asystole may result if the ventricular rate is significantly slowed without attainment of regular atrioventricular conduction, procainamide should be stopped and the patient re-evaluated.

In the presence of both liver and kidney damage, normal dosage may produce symptoms of overdosage—principally ventricular tachycardia and severe hypotension.

A syndrome resembling lupus erythematosus has been reported with oral maintenance procainamide therapy. Common symptoms are polyarthralgia, arthritis and pleuritic pain. Fever, myalgia, skin lesions, pleural effusion and pericarditis may also occur. Rare cases of thrombocytopenia or Coombs-positive hemolytic anemia, possibly related to this syndrome, have been reported. Measure anti-nuclear antibody titers at regular intervals in patients on procainamide for extended periods of time or in whom symptoms suggestive of lupus-like reaction appear; in event of rising titer (anti-nuclear antibody) or clinical symptoms of LE, assess the benefit/risk ratio related to continued procainamide therapy (see boxed Warning). Steroid therapy may be effective if discontinuation of procainamide does not cause remission of symptoms. If the syndrome develops in a patient with recurrent life-threatening arrhythmias not otherwise controllable, steroid-suppressive therapy may be used concomitantly with procainamide.

ADVERSE REACTIONS: Hypotension is rare with oral administration. Serious disturbances of cardiac rhythm such as ventricular asystole or fibrillation are more common with I.V. administration.

Large oral doses may sometimes produce anorexia, nausea, urticaria, and/or pruritus.

A syndrome resembling lupus erythematosus has been reported in patients on oral maintenance therapy (see Precautions). Reactions consisting of fever and chills have been reported, including a case with nausea, vomiting, abdominal pain, acute hepatomegaly, and a rise in serum glutamic oxaloacetic transaminase following single doses of the drug. Agranulocytosis has been occasionally reported following repeated use of the drug, and deaths have occurred. Therefore, routine blood counts are advisable during maintenance procainamide therapy; and the patient should be instructed to report any soreness of the mouth, throat or gums, unexplained fever or any symptoms of upper respiratory tract infection. If any of these symptoms should occur and leukocyte counts indicate cellular depression, procainamide therapy should be discontinued and appropriate treatment should be instituted immediately. Bitter taste, diarrhea, weakness, mental depression, giddiness, psychosis with hallucinations, and hypersensitivity reactions such as angioneurotic edema and maculopapular rash have been reported.

For full prescribing information, consult package insert.

HOW SUPPLIED: Pronestyl Tablets (Procainamide Hydrochloride Tablets) providing 250 mg, 375 mg, and 500 mg procainamide hydrochloride are available in bottles of 100 and Unimatic® single-dose packaging in cartons of 100. The 250 mg and 500 mg tablets are also available in bottles of 1000.

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THE WESTERN
Journal of Medicine

Refer to: Osborne CK, McGuire WL: Therapy for cancer of the breast—Current status of steroid hormone receptors. West J Med 130:401-407, May 1979

Therapy for Cancer of the Breast

Current Status of Steroid Hormone Receptors

C. KENT OSBORNE, MD, *and* WILLIAM L. McGUIRE, MD, *San Antonio, Texas*

Estrogen receptor (ER) assays in human breast cancer tissue have proved useful in selecting patients for endocrine therapies. The absence of ER indicates hormone independent tumors and precludes the use of endocrine therapy. Patients with positive tumor ER respond to endocrine therapy at nearly twice the rate of those patients chosen by clinical criteria, although about a third of ER positive tumors in patients still do not respond. Recently, research has been directed toward increasing the accuracy of the ER assay in the ER positive group. The absolute tumor ER value and the presence of progesterone receptor appear promising in this regard. The significance of nuclear estrogen receptor is being studied. Finally, the ER status of a primary breast tumor appears to be a marker for the length of time until recurrence after mastectomy, and for survival. The ER assay may prove valuable in planning new adjuvants in the treatment of breast cancer.

BREAST CANCER is the most prevalent form of cancer and cause of death in women today. Each year about 90,000 new cases are diagnosed and more than 30,000 women die from cancer of the breast. Despite the frequency of this disorder, until recently there have been few major advances in our understanding of the disease and its treatment. Even the surgical treatment of breast cancer remains controversial, in spite of the fact that various radical surgical therapies have been practiced for almost a century. Similarly, progress in other forms of treatment has been slow, partly because there have been few clinical and laboratory investigations of the many problems common to this type of tumor.

A good example is the hormone *dependence* of breast cancer. More than 80 years ago Beatson showed that ovariectomy caused tumor regression in certain women with breast cancer, demonstrating that hormones influence the growth of these tumors. Since normal mammary tissue is thought to be a target for the action of many hormones, it is not surprising that malignant mammary cells may retain this hormonal influence. It is now recognized that a variety of ablative and additive hormone therapies may cause tumor regression and significant palliation for certain patients. This intriguing relationship between hormones and breast cancer engendered a wave of empirical investigation. Yet, only about 30 percent of women

From the Department of Medicine, The University of Texas Health Science Center at San Antonio.

Submitted December 6, 1978.

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ABBREVIATIONS USED IN TEXT
ER = estrogen receptor
PgR = progesterone receptor

with breast cancer respond to modern hormonal manipulation. Whereas those patients responding to therapy frequently have many months of remission and prolonged life, most fail to respond and, therefore, receive ineffective therapy, and sometimes radical ablative surgical procedures associated with increased morbidity. Clinical characteristics such as age, menopausal status, disease-free interval after primary treatment and sites of tumor involvement have not notably improved our ability to select patients likely to benefit from these treatments.

Because in two of every three patients with metastatic breast cancer there is no response to endocrine manipulation, it is easy to understand the recent popularity of combination chemotherapy as the primary therapy. In 50 to 70 percent of patients chemotherapy now results in response, with median durations of remission approaching one year. Unfortunately, those patients who would have had a prolonged remission with a simpler, less toxic hormone therapy are excluded in this approach. It is obvious that an accurate method for selecting those patients who are likely to respond to endocrine therapy would be highly desirable.

Recently, basic research into the biochemical mechanism of hormone action in breast cancer has been rewarded with great improvements in treatment. Although overall numbers of patients responding to endocrine therapies have not changed, the selection of patients most likely to respond has greatly improved. It is now established that measurement of estrogen receptor (ER) protein in breast cancer tissues enhances a clinician's ability to predict the hormone dependence or independence of a patient's tumor.[1] In this article, we will summarize current knowledge concerning the biochemical mechanisms of hormone action in human breast cancer, while emphasizing the role of hormone receptor assays in a rational approach to the management of patients with this disease.

Mechanism of Steroid Hormone Action

To understand the rationale for the measurement of ER in breast cancer, a brief review of the biochemical events in steroid hormone action is necessary. All steroid hormones are lipid soluble and

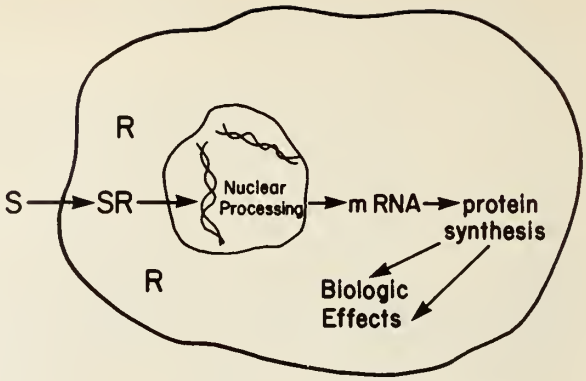

Figure 1.—Steps in steroid hormone action. S = any steroid hormone. R = cytoplasmic receptor protein.

easily diffuse across cell membranes into the cytoplasm. In target tissues (cells biologically responsive to a hormone), protein molecules (receptors) in the cytoplasm bind the steroid hormone with high affinity and specificity (Figure 1). These receptors concentrate the hormone inside the target cell where the receptor-steroid complex is promptly translocated to the nucleus. The complex binds to chromatin acceptor sites and through an unknown mechanism alters transcription and the synthesis of specific messenger RNA. These altered patterns of synthesis of translatable messenger RNA then affect protein synthesis at the level of the ribosome, with subsequent changes in specific cell processes. Although the events distal to receptor binding are not completely defined, it is generally agreed that receptor binding is coupled with the biologic effect. Absence or loss of the hormone receptor, or a block or defect in the sequence of events distal to binding, results in the inability of the cell to respond to the hormone. Therefore, the absence of estrogen receptor in breast cancer cells should preclude any direct effects of estrogens on the cell.

Historical Perspective

Soon after it was shown that when radioactive estrogen was injected *in vivo* into animals it localized in normal target tissues,[2] it was observed that a larger fraction of injected radioactive estrogens concentrated in breast tumors in patients responding to hormone therapy than in patients who did not respond.[3] Similar observations were made in experimental animals with mammary cancer, and were extended to show that excised tumors *in vitro* also concentrated more hormone

if they were hormone responsive tumors than if they were not. This led to the proposal that an *in vitro* test might be developed for human tumor biopsy specimens to predict responsiveness to hormone therapy. The discovery that a cytoplasmic receptor protein was responsible for the specific uptake of estrogen by target cells raised the possibility that measurement of the receptor protein itself might predict the hormone dependence of the tumor.[4] Numerous techniques were developed and used to measure estrogen receptor in human breast cancer specimens. Detailed methodology and the advantages and disadvantages of these techniques have been reviewed before.[1] Nevertheless, in the early 1970's, several researchers using a variety of methods measured ER in human breast tumor specimens and collected data correlating clinical response with the assay results. In 1974 an international workshop was held at the National Institutes of Health to review the results. Several international laboratories using different techniques produced a strikingly similar pattern of results, and showed that estrogen receptor assays were valuable in predicting results of endocrine therapy in patients with metastatic breast cancer.[1]

Estrogen Receptors in Breast Cancer

Although controversy persists regarding some of the conclusions drawn from early studies on estrogen receptors in breast cancer, several comments can be made.

General Characteristics

Estrogen receptors in human breast cancer specimens have qualities similar to those in other human and animal target tissues. Most important, they have high binding affinity and steroid hormone specificity. Biologically inactive estrogens or other classes of steroid hormones bind poorly, or not at all, to ER. Receptor concentration in tumor specimens varies over a wide range up to more than 1,000 femtomoles per mg of cytosol protein.[4] This range, although not totally understood, has been attributed to a combination of factors, including tumor cell heterogeneity (the ER value varies with the proportion of tumor cells that contain receptor) or endogenous estrogen levels (the lower the estrogen level, the greater the level of unbound and therefore measurable receptor present in the cytoplasm). The latter factor may also partially explain the general observation that postmenopausal women not only have a greater proportion of receptor positive tumors, but also have higher tumor ER concentrations.

Tumor Histology

Early studies suggested that the level of ER did not correlate with tumor histology, although the more undifferentiated tumors had a slightly greater proportion of negative assays.[1] Recently, however, a high frequency of positive ER assays has been described in invasive lobular carcinoma, whereas tumors with notable local lymphocyte reaction were less frequently ER positive.[5] The lack of a correlation between tumor response to endocrine therapy and tumor histology (particularly lobular carcinoma) reported in the older literature raises questions concerning the validity of these data. Perhaps these discrepancies are due to difficulties inherent in the histopathologic classification of breast cancer, the relatively small number of patients with lobular carinoma or real biological alterations of the cells that make up this tumor type.

Primary Versus Metastatic Tumor

Another interesting observation is that there is a difference between the proportion of positive ER assays in primary specimens and in metastatic specimens. It is generally agreed that primary tumors are more often receptor-positive than metastatic tumors (77 percent versus 66 percent in our series).[4] One explanation is that breast tumor cells may become less differentiated and lose normal endocrine control mechanisms as a function of the duration of disease. Alternatively, hormone-independent cells in a heterogeneous primary tumor may become the dominant cell type in time, as a result of selective growth kinetics or other biological advantages. Preliminary data from a few patients having multiple sequential biopsies during the course of their disease and showing a progressive quantitative decrease in ER level may be similarly explained,[6] although the effect of endocrine or drug therapies on tumor ER must also be considered.

Tumor Size

Data correlating ER level with size of the primary tumor are conflicting. Early studies showed a negative correlation between tumor size and the presence of ER.[1] It was suggested that larger tumors were more likely to have necrotic areas resulting in less receptor. An alternative explana-

tion is that larger tumors have undergone more cell divisions and have selected out ER negative cells, or have become less differentiated and have lost receptor. Other studies have failed to show a statistically significant relationship between these factors.[5]

Miscellaneous Factors

There is general agreement that clinical stage of disease, axillary node status and tumor location in the breast do not correlate with the presence of ER. In addition, the duration of remission with endocrine therapy does not correlate with the absolute ER level. There is insufficient information regarding ER levels in multiple simultaneous tumor biopsies from different sites in the same patient to draw firm conclusions.

Correlation with Endocrine Therapy

Convincing data suggesting that ER assays in breast tumors help to predict response to hormone therapy were presented at an international workshop on estrogen receptors in 1974.[1] More than 400 treatment trials from 14 institutions, using different methods for ER assay, were evaluated by independent reviewers and the results were pooled. The general pattern of results was surprisingly similar for all of the participating institutions, and has been confirmed by subsequent independent studies. The collective data are summarized in Table 1. Tumors containing ER have a 55 percent to 60 percent response rate to both ablative and additive hormone therapies. This response rate is about twice the rate for patients selected using only clinical criteria. A more striking result is seen in ER negative tumors. Only about 8 percent of this group responds to endocrine therapy. In several subsequent studies this result has been confirmed with only 5 percent to 10 percent of ER negative tumors responding to hormone manipulation. The results of this initial series are not as striking for patients undergoing hypophysectomy or antiestrogen therapy. However, more recent experience with larger numbers of patients shows a good correlation between receptor status and clinical response to these modalities. Therefore, although a positive estrogen assay notably increases a clinician's ability to correctly select patients likely to respond to endocrine therapy, about a third of these patients fail to respond. On the other hand, clinicians can exclude confidently those patients with negative assays from any endocrine therapy. In recent years investigation has been directed toward increasing the accuracy of ER assays in the receptor-positive group.

TABLE 1.—*Objective Tumor Regression With Endocrine Therapies as a Function of Estrogen Receptor Status*

Therapy	*ER+ Tumors*	*ER− Tumors*
ABLATIVE		
Ovariectomy	23/33	4/53
Adrenalectomy	32/66	4/33
Hypophysectomy	2/8	0/8
TOTAL	59/107=55%	8/94= 8%
ADDITIVE		
Estrogen	37/57	5/58
Androgen	12/26	2/24
Glucocorticoid	2/2	....
TOTAL	51/85 =60%	7/82= 8%
MISCELLANEOUS		
Antiestrogens	8/20	5/27
Other	2/3	0/5
TOTAL	10/23 =43%	5/32=26%

ER = estrogen receptor

Quantitative Levels of ER

Preliminary observations suggested a poor correlation between the absolute level of ER and response to endocrine therapy.[1] However, one might expect that a heterogeneous tumor containing more ER positive cells, and consequently having a higher ER level, might be more responsive to endocrine therapy. Our most recent analysis of 111 patients with receptor assays on metastatic biopsies, and in whom various endocrine therapies have been carried out, supports this hypothesis.[7] Only 6 percent of tumors with absent to low ER levels (0 to 3 femtomoles per mg of protein) responded to therapy, whereas 50 percent of tumors with intermediate levels (3 to 100 femtomoles per mg of protein) and 80 percent with high levels (101 to 1,000 femtomoles per mg of protein) regressed. These data suggest that the quantitative analysis of tumor ER identifies subgroups of patients with clearly different response rates, further enhancing our ability to select patients for endocrine therapy.

Nuclear Estrogen Receptor

Several explanations may account for the observation that about a third of ER positive tumors do not regress with hormone therapy. As shown in Figure 1, a defect at any step in the mechanism of estrogen action might render the cell unrespon-

sive to estrogen. Present data suggest that the absence of receptor results in a hormone independent cell. However, cells containing receptor might also be hormone independent if the receptor is abnormal, if nuclear translocation of the receptor-estrogen complex is blocked, or if nuclear events (processing) or steps distal to processing are defective. With this in mind, one might propose that an assay to determine the functional integrity of the estrogen response pathway might improve the selection of estrogen dependent tumors. For instance, detection of nuclear estrogen receptor bound to estrogen would suggest that receptor binding and translocation to the nucleus were intact. Recently, our laboratory has developed assays for nuclear estrogen receptor in human breast tumor samples.[7] Although sufficient samples have not yet accumulated to assess the correlation with response to therapy, several observations have been made: First, certain tumor specimens contain cytoplasmic and nuclear estrogen receptors, perhaps indicating a functional endocrine-response system. Second, a few tumors containing cytoplasmic ER have no detectable nuclear ER, and it is not yet known whether these tumors are estrogen independent. Finally, we observed that certain tumors contained nuclear receptor that was not bound to estrogen (*free* nuclear receptor), a phenomenon not observed in normal target tissues. The function of this free nuclear receptor will require further study. It is tempting to speculate that cytoplasmic ER in some malignant breast cancer cells can enter the nucleus and promote growth or other estrogenic effects, even in the absence of estrogen. Such tumors would not respond to additive or ablative estrogen therapy, despite a positive assay for cytoplasmic receptor. On the other hand, these tumors might respond to antiestrogens, which could bind to, and functonally turn off, the estrogenic activity of these *free* receptors.

Progesterone Receptors in Breast Cancer

Measurement of cytoplasmic progesterone receptor (PgR) has been proposed as another method of determining an intact estrogen response pathway, and providing a better indication of breast tumor hormone dependence.[4,7] The rationale for this proposal evolved from extensive investigations in animal uterine tissue, showing that estrogen controls the synthesis of PgR. Thus, the presence of PgR in a breast tumor specimen might indicate that all of the steps in the mechanism of estrogen action were intact. Recently our laboratory and several others have been measuring ER and PgR in breast tumor specimens and correlating the results with response to hormone therapy. Although this approach must still be considered experimental and must not be recommended for routine use, the data from limited numbers of patients suggest that the PgR assay increases our ability to choose patients for endocrine therapies. First, in support of our hypothesis that estrogen might control PgR synthesis in cancer of the breast, we found that PgR is rarely detected in ER negative, and therefore estrogen independent, tumors (Table 2). In fact, receptor assays in more than 100 metastatic tumor specimens show that 33 percent have neither receptor; only 1 percent have PgR in the absence of ER; 27 percent have ER without PgR, and 39 percent have both. Those tumors with ER and PgR should have a higher response rate to hormone therapy; preliminary data pooled from two laboratories support this contention (Table 3). No tumors deficient in ER and PgR regressed with treatment, whereas more than 80 percent of tumors containing both receptors regressed. A much smaller proportion of tumors with ER but not PgR were hormone dependent. It is interesting to speculate that the patients in whom there was response in the latter group had a negative PgR assay, not because of a defect in the mechanism of estrogen action, but because of insufficient circulating estrogen to stimulate PgR synthesis. Perhaps short-term stimulation, with estrogen *in vivo* before biopsy to

TABLE 2.—*Distribution of ER and PgR in Metastatic Human Breast Cancer*

Receptor Status	*Percent of Total*
ER− PgR−	33
ER− PgR+	1
ER+ PgR−	27
ER+ PgR+	39

ER = estrogen receptor
PgR = progesterone receptor

TABLE 3.—*Objective Regression of Metastatic Breast Cancer as a Function of ER and PgR*

Receptor Status	*Number Patients*	*Number Remissions (Percent)*
ER− PgR−	17	0(0)
ER− PgR+	1	1(?)
ER+ PgR−	24	7(29)
ER+ PgR+	29	24(83)

ER = estrogen receptor
PgR = progesterone receptor

TABLE 4.—*Recurrence Rates According to ER Status*

Patients	Number Patients	Recurrence at 18 months ER−	ER+
Total	145	19/54 (35%)	13/91 (14%)*
Node− ...	71	3/25 (12%)	3/46 (6%)
Node+ ...	74	16/29 (55%)	10/45 (22%)*

ER = estrogen receptor

*Horizontal comparison, $p < 0.05$

stimulate PgR, might identify this group of patients. In any case, these encouraging results need confirmation.

Estrogen Receptors and Prognosis of Patients With Breast Cancer

Recently, further analysis of ER data in patients with primary operable breast cancer has suggested another use for the ER assay. In 145 patients with surgically treated primary breast cancer, there was a faster rate of recurrence in patients with ER negative tumors than in those with ER positive tumors (Table 4).[7,8] In fact, 18 months after mastectomy, cancer recurred in 34 percent of the ER negative group, compared to 14 percent of the ER positive cases. When these patients were classified according to their axillary node status, the pattern of results was unchanged; in a greater number of ER negative patients cancer had recurred. Also, regardless of the patient's age or menopausal status, the size or location of the breast tumor, or the administration of postoperative adjuvant radiotherapy or chemotherapy, the disease-free interval was notably shorter in patients with ER negative primary tumors. Therefore, the ER status of a primary breast tumor appears to be an important indication of the length of time until recurrence, independent of other known prognostic variables. Preliminary observations suggest that survival is also adversely affected in ER negative patients. Although these findings require confirmation, we propose that the ER status of a primary tumor may help in planning new adjuvants in the treatment of breast cancer.

Use of Receptor Assays in the Rational Approach to Therapy

The role of the assay for cytoplasmic ER to predict the hormone responsiveness of a tumor is well established. With this and the preliminary data discussed above in mind, we have formulated a possible approach to the treatment of primary and metastatic breast cancer (presented in Figures 2 and 3). After appropriate local therapy for

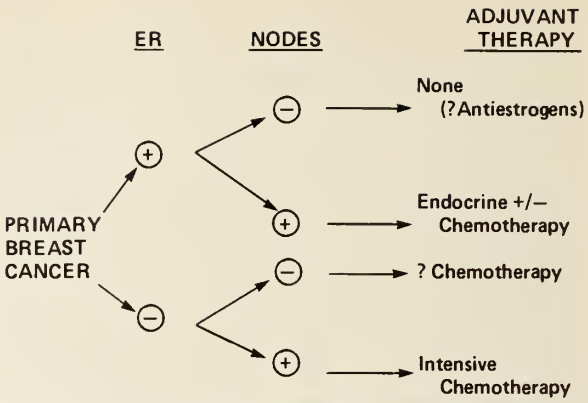

Figure 2.—Schematic approach to the adjuvant treatment of primary breast cancer. ER = estrogen receptor.

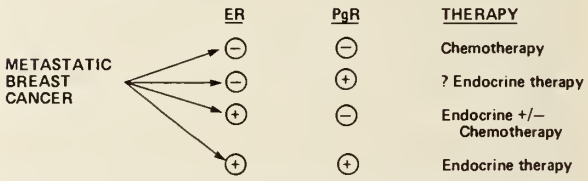

Figure 3.—Schematic appoach to the treatment of metastatic breast cancer. ER = estrogen receptor. PgR = progesterone receptor.

primary breast cancer, patients are categorized according to their ER and axillary node status (Figure 2). These factors indicate prognoses and aid in selecting appropriate adjuvant therapy. Patients with ER positive tumors and microscopically negative axillary nodes have the least aggressive disease and the best chance for cure. Perhaps these patients should receive no additional treatment. However, a small percentage of these patients have clinically silent micrometastases at the time of diagnosis, and tumors will recur. For this ER positive group, adjuvant endocrine therapy with an antiestrogen might save patients destined to have relapses, without giving them more toxic, sometimes unnecessary, chemotherapy. Patients with axillary node involvement from ER positive tumors have a less favorable prognosis. Since residual microscopic tumor cells are likely to be hormone dependent, these patients should be considered for adjuvant endocrine therapy. The use of chemotherapy might also be considered because certain tumors may not be hormone responsive, despite the presence of ER, and because the tumor may include some receptor negative cells. Although success with adjuvant hormone therapy in the past has been limited to slight prolongation of the disease-free interval after surgical operation, rather than to improved length of survival, pa-

tients were not selected according to their tumor receptor status, making the results difficult to interpret with our present knowledge. Patients with ER negative tumors are not likely to benefit from hormone manipulation. Adjuvant chemotherapy might be reserved for this group of patients, regardless of the axillary node status in view of the more aggressive nature of this tumor.

Decisions regarding therapy for patients with previously untreated metastatic breast cancer should be guided by the clinical setting and the tumor receptor status (Figure 3). Chemotherapy is appropriate for patients with ER and PgR negative tumors because endocrine therapy is rarely effective. Although ER negative, PgR positive patients are rare, our current hypothesis suggests that tumors in these patients might be hormone dependent, and that the ER assay is falsely negative with ER bound in the nucleus and not measured by routine assays. The choice of therapy for patients with positive ER but negative PgR tumors is a dilemma. About 30 percent respond to endocrine therapy. It is hoped that further advances in assay technique will improve our ability to select these patients. Patients without life-threatening visceral metastases might be given endocrine therapy, with chemotherapy reserved for patients in whom treatment fails and patients with advanced visceral disease. Finally, endocrine therapy should be considered for all patients with positive ER and PgR assays. In the few patients in this group with brain or lymphangitic lung metastasis, intensive chemotherapy could be combined with hormone manipulation.

It should be emphasized that this schema is tentative at present and represents one attempt to devise new treatment programs more rationally for breast cancer patients. This should not be interpreted as the only approach to the treatment of this disease, but as a direction for future clinical trials. Although the value of ER assays is established, more data are needed confirming our preliminary observations that quantitative ER levels, PgR or nuclear estrogen receptor assays may be valuable in predicting hormone dependent tumors. Further research into the basic biochemical mechanisms of hormone action in breast cancer should continue to improve the clinical management of this disease.

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Refer to: Ripley HS: Suicide in general hospitals. West J Med 130:408-410, May 1979

Suicide in General Hospitals

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Of 14 medical and surgical patients who committed suicide in a general hospital, there were ten men and four women, ranging in age from 19 to 82. The patients had not made statements of suicidal intent; however, their hospital records showed there had been symptoms of depression and contained indirect references to a preoccupation with suicide. Most of the patients had been depressed because of their illnesses or distressing symptoms.

It is important to keep in mind that there are clues that help anticipate suicide. Awareness by hospital staffs of symptoms and subtle signs of depression and of suicidal thoughts in patients is important in reducing the number of suicides in general hospitals. Of preventive and treatment measures, warmth, compassion and commitment to the care of patients by hospital staffs are most important.

WHEN A PATIENT in a general hospital commits suicide, there generally has been a failure by the staff to see signs or symptoms of depression, and therefore a failure to institute preventive measures. In patients who have not shown signs of depression or suicidal intent, recognizing this intent is especially difficult and members of the hospital staff should be aware of indications of psychiatric illness. Because there have been relatively few studies of suicide in medical and surgical departments, other than that by Pollack,[1] further analysis of the problem is needed.

During a ten-year period in a general hospital where a high percentage of the patients in other departments were referred to the psychiatric liaison department,[2] 14 medical or surgical patients with whom consultations had not been requested killed themselves. More than a fourth of the patients (150) seen in consultation for psychiatric problems were found to be depressed.[3] However, none of them committed suicide. Collaborative treatment by the medical and surgical staff and the psychiatric consultant was carried out in all patients, except in 12 who were transferred to the psychiatry department.

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Methods and Symptoms

Among the 14 patients not seen by a psychiatrist, 12 jumped from windows, one cut his throat and another stabbed himself. (Of Pollack's 11 patients, ten jumped from windows and one cut his throat.[1]) There were ten men and four women, aged 19 to 82, with widely varying illnesses. Four patients had malignant conditions with unfavorable prognoses and three had other terminal illnesses. In seven patients the prognosis was considered *fair* to *excellent* for recovery; of these, two had cardiovascular disease and the other five had peptic ulcer, hyperthyroidism, sciatica, acute cholecystitis or fractures from an

automobile accident. During the ten years one patient in the psychiatric department committed suicide by hanging.

The hospital records of the patients who committed suicide contained notes made by physicians or nurses showing some evidence of depression in each case: "The patient has become apathetic. He seems to have lost the desire to get well." "He is waking up early and seems worse in the morning than the evening." "There is no desire for food." Direct or indirect communication of suicidal preoccupation was illustrated by such remarks from patients as "I cannot bear this pain much longer," "I'm never going to get well," "I won't be here tomorrow" or "I have lived long enough."

Clinical Syndromes

Psychiatric diagnoses were not clear in some cases, but it seemed from the information available that most of the patients had neuroses resulting from: (1) serious or even fatal illnesses, (2) delusions of having an illness with a poor prognosis, (3) distress because of pain, nausea, vomiting, respiratory difficulties, and disabilities of movement or (4) fear of suffering or death. Three patients showed symptoms of such a mild degree of psychotic depression that diagnosis was uncertain. In two patients some clouding of the sensorium indicated an organic brain syndrome caused by a toxic or structural condition. These findings contrast those of Pollack[1] who analyzed the clinical records of 11 men, medical and surgical patients, who committed suicide in a Veterans Administration teaching hospital. He concluded that seven of the patients had unrecognized organic psychoses and two of the patients had functional, or possibly functional, depressive psychoses. The presumed cause of suicide in another patient was a reaction to extreme pain and physical disability, and the presumed cause in the 11th patient was depression resulting from physical disease in an emotionally unstable, anxious personality.

Danger Signals

In a previous report[4] the evaluation and management of suicidal behavior has been discussed in some detail. Physicians, nurses, aides and social workers on a ward should recognize the danger signals often preceding suicidal behavior. The staff's vigilance can help prevent suicides by making it possible to institute immediate precautionary measures, treatment and psychiatric consultation.

Because some degree of depression (varying from a mood of depression to a neurotic reactive depressive illness to a severe depressive psychosis) is present in a high percentage of those patients with suicidal behavior (ranging from suicidal gestures to actual suicide), it is important to be aware of the common symptoms of a depressive reaction. The more severe the depression, the more likely a patient is to complete the act. The most common emotional and cognitive manifestations of depression are sadness, self-depreciation, hopelessness, crying, diurnal mood variation, decreased libido, indecisiveness, poor concentration, suicidal preoccupation, apathy, and hypochondriasis or even somatic delusions. In the most severe depressive illnesses, delusions of worthlessness, sinfulness or poverty, and auditory hallucinations of condemnation may occur. The most common physical manifestations of depression are pain, insomnia, fatigability, anorexia, weight changes, constipation, psychomotor retardation or agitation, and lowered metabolism. In adolescents, boredom, difficulty in concentrating, fatigue, insomnia and hypochondriasis are frequent symptoms of depression.[5] Often only some of the symptoms are present.

In some patients there may be underlying depression with no affective symptoms, but with complaints of weight loss, insomnia and pain—which can often be equivalents of depression. The nature of such a masked depressive illness has been confirmed by favorable responses in such cases to therapy with antidepressant medications or electroshock treatments. It should be emphasized that just as symptoms of depression may mask organic disease, physical symptoms of disease may mask depression.[6]

Other Clues

In addition to indirect references to suicide and the symptoms of depression, there are other valuable clues to potential suicides. Disoriented patients may respond to delusional or hallucinatory commands to kill themselves. Patients who are irritable, demanding or uncooperative, frequently have underlying hostility toward themselves, which may lead to suicidal action. These patients tend to alienate the staff but frequently respond well to extra attention. When suicidal ideas are suspected, gentle and tactful questioning may bring out suicidal ideation. Talking about suicide is apt to decrease rather than increase the risk of suicide by giving a patient an opportunity to discuss his

thoughts and feelings with a confidant. Patients who have had close friends or relatives die, or who have lost status, health, money, physical appearance or function, are especially susceptible to suicidal behavior. In previous studies of suicides and attempted suicides,[7,8] loss of health was shown to be a frequent cause, surpassed only by loss of loved ones.[9] Previous attempted suicides are indications of a higher risk.

High-Risk Groups

Although there is no substitute for knowing a patient well, data based on probability are valuable in considering suicidal risk. The highest incidence of suicide occurs in the following categories: men; people who are divorced, separated or widowed; drug abusers or excessive users of alcohol; unemployed persons; those with poor living conditions; persons who are physically or psychiatrically ill; members of the white race, and those in the older groups. However, in recent years growing numbers of young people have committed suicide; for those between ages 15 and 24, the rate rose between 1957 and 1975 from 4.0 to 10.5 suicides per 100,000.

Precautions

A number of precautions should be carried out. Because many suicides in hospitals are committed by patients jumping from windows, safety screens should be used. Sharp objects, such as knives, blades and glass, and material that could be used for hanging oneself, such as ropes, neckties and belts, should be removed. Patients should be checked frequently and receive solicitous attention from nursing personnel. A few patients will need the protection and treatment provided by a psychiatric department.

Treatment

The main approaches to treatment are psychotherapy, electroshock, and administration of antidepressant and tranquilizing drugs. Use of electroshock treatment should be reserved for those in whom other types of therapy are not effective.

Psychiatric consultation should be requested for patients suspected of having suicidal thoughts, those who have already expressed them, and those who have made suicide attempts—even though the attempts do not seem serious. With suggestions from a psychiatrist the concerned family physician can best care for most suicidal general hospital patients. Patients with severe psychotic depressions, and those needing intensive personality analysis or electroshock therapy, should be treated by a psychiatrist. Appropriate medications can be prescribed by a physician who is familiar with the patient's behavior.

Crucial to preventing suicidal behavior is the dedication of nurses, social workers, and physicians during the patients' hospital stay. Constructive, sustaining relationships may be developed with people in any of these professional categories.

After a patient's discharge from the hospital, the physician needs to be available for phone calls, even in the middle of the night, and frequent, even daily visits, as long as the danger of suicide exists. The patient should be allowed to express his feelings without dwelling on morbid ideas, and he should be reassured that based on our knowledge the prognosis for depressive illnesses is excellent. Physicians should suggest that a depressed patient use recreational and occupational diversions geared to the patient's ability to concentrate.

For a depressed patient, the loss of the patient-physician relationship, or a threat of losing it, may be the final trauma leading to suicidal behavior. Because treating depressed patients is likely to be stressful and wearing, a physician should not become involved if he does not wish to treat the patient, or does not feel he can devote sufficient time. If a practitioner does not assume responsibility for treatment of a suicidal patient, he can refer the patient to a psychiatrist or to a mental health, suicide prevention or crisis clinic. If he does assume responsibility for treatment, he must offer all the resourcefulness and dedication he would give in any other life-and-death situation. For most patients the practitioner's credentials or expertise matter less than does his capacity for warmth, compassion and emotional commitment.

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Marital and Reproductive Histories of Women With Cancer of the Breast and Their Sisters

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In a study of 45 pairs of sisters—each pair including one sister with cancer of the breast and one without the disease—differences in marital and reproductive histories were observed. These differences included less frequent marriage, later marriage, fewer children, and a longer delay between date of marriage and the first pregnancy in the sisters with the disease. These findings appear to confirm presently known reproductive risk factors for cancer of the breast, but they also raise the possibility that unknown behavioral factors influencing the endocrine system may be delaying marriage and pregnancy.

A NUMBER OF ARTICLES[1-5] have reported an association between the risk of cancer of the breast and women's reproductive histories. This association is based primarily on retrospective studies that compared hospital patients having cancer of the breast to patients with other diseases for such variables as age, race and socioeconomic status. Lilienfeld and associates[5] used as controls healthy women from the same community as the women with cancer of the breast in studying the epidemiology of the disease. Closer comparisons can be achieved by using siblings, one with and one without the disease. Members of the same family are more similar genetically and socioculturally than the cases and controls in studies cited above. Henderson and co-workers[6] published a study on marital and reproductive histories of patients and their sisters but did not consider the possible effect of birth order on their findings.

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This article describes the findings of a small study of 45 pairs of sisters, each pair including one sister with and one without a cancer of the breast. In approximately half of the pairs the patients were older than their sisters. This allowed us to take the order of birth of the patients and their sisters into account as we compared their ages at the time of marriage, through the history and frequency of term pregnancy, and during the interval between marriage and first term pregnancy.

Patients and Methods

Questionnaires were distributed at a meeting of the Marin Mastectomy Service,* Marin County, California, to women in whom cancer of the breast had previously been diagnosed. Information was requested on the marital and reproductive history of the patient and that of a sister without the disease who was nearest to the patient in age. Eighteen pairs of completed questionnaires were received from this group.

Similar information was requested from a group

*This organization's cooperation was important to the study.

of patients with cancer of the breast seen at the University of California, San Francisco, either during a follow-up examination or at the time of the initial diagnosis. Completed questionnaires were received from 27 of these patients and their siblings, bringing the total number studied to 45 pairs of sisters.

Results

Characteristics of the Study Group

Cancer of the breast in patients in this study was diagnosed between 1960 and 1976, except for one case that was diagnosed in 1949. The group was composed of 37 pairs of whites, five pairs of blacks, two pairs of Asians, and one pair of sisters whose race was not recorded. At the time of the study, the patients had a mean age of 51.6 years and a median age of 53.0 years. The sibling was older than the patient in 22 pairs (mean difference in age of 4.2 years and a median difference of 3.5 years), younger in 22 pairs (mean difference of 4.2 years and a median difference of 3.0 years). The remaining pair of sisters was twins.

Age at Marriage

Tables 1 and 2 show the ages of the patients and their sisters at the time of marriage. Six of the patients and three siblings in this study did not marry. As shown in Table 1, the mean age at the time of marriage for the 39 patients was 26.3 years and 22.6 years for their sisters ($p<.01$). The patients married at a later age than their sisters, whether they were older or younger than the sisters; this excludes order of birth as a factor in their later marriages. Table 2 shows findings for the 38 pairs in which both had been married. The mean age at the time of marriage for patients was 4.1 years greater than the mean age for the sisters ($p<.001$). The findings were similar both when patients were older and when the sisters were older. Similar patterns were noted when the median ages at the time of marriage were reviewed.

In five of the 38 pairs in which both were married, the recorded ages at the time of marriage were the same. Of the 33 pairs in which the members were married at different ages, the patient was married at a later age in 26 of the pairs ($p<.001$). The patient was married at a later age in 16 of 19 instances where the sister was younger, and in ten of 14 instances where the sister was older.

Reproductive History of Patients and Their Sisters

When we calculated our results, we used Lilienfeld's definition of "term pregnancy"[5]—a pregnancy of at least four months' duration. Of the 38 pairs in which both members were married, 34 sisters (Table 3) experienced at least one term pregnancy compared with 26 of the patients ($p<.05$). This pattern primarily applied to pairs in which the patient was older than the sister. There were 12 pairs in which one member of the pair had at least one pregnancy and the other did not. In ten of these 12 pairs, it was the patient who had no pregnancies ($p<.02$).

For the 24 pairs in which both members were married and both had term pregnancies (Table 4), the mean interval between the time of marriage and the first pregnancy was longer for patients (three years) than for their sisters (one year) ($p<.10$). This pattern was again noted both when the patient was older than the sister and when the sister was older than the patient. A similar finding was noted when the median interval between marriage and the first pregnancy was studied.

Table 5 shows that the sisters tended to have

TABLE 1.—*Age at Marriage by Birth Order (all members who had married)*

	*All Pairs**		*Patient Older*		*Patient Younger*	
	Patients	*Sisters*	*Patients*	*Sisters*	*Patients*	*Sisters*
Mean age (years) ...	26.3	22.6	26.5	21.6	26.0	23.7
No. of individuals.	39	42	20	20	19	21

*Includes one set of twins.

TABLE 2.—*Age at Marriage by Birth Order (both members married)*

	All Pairs		*Patient Older*		*Patient Younger*	
	Patients	*Sisters*	*Patients*	*Sisters*	*Patients*	*Sisters*
Mean age (years) ...	26.5	22.4	27.1	21.1	26.0	23.7
No. of pairs .	38		19		19	

TABLE 3.—*History of Term Pregnancy by Birth Order (both members married)*

	All Pairs		*Patient Older*		*Patient Younger*	
History	*Patients*	*Sisters*	*Patients*	*Sisters*	*Patients*	*Sisters*
Term pregnancy .	26	34	12	19	14	15
No term pregnancy .	12	4	7	0	5	4
TOTAL	38	38	19	19	19	19

more term pregnancies than the patients with a mean of 2.6 for the sisters, and 1.7 for the patients ($p<.01$). This pattern is also found when birth order is taken into account and also when the median values are examined.

Table 6 summarizes the relative number of term pregnancies of patients compared with their sisters. The patient had fewer term pregnancies than the sister in 24 of 33 pairs ($p<.01$) in which differences in the number of term pregnancies were noted. Again, birth order was not a factor.

Age at Menarche and Contraceptive Practices

The distribution of recorded ages at menarche was essentially the same for both the patients and their siblings. There was no suggestion of differences in contraceptive practices between patients and controls from responses to the questionnaires in this limited study.

Discussion

A number of studies, primarily using hospital patients with other diseases as controls, have reported a higher percentage of breast cancer patients who were never married. Those with cancer of the breast who did marry, married at an older age, waited longer to have the first child and had fewer term pregnancies than those who did not have the disease. By using sisters as controls, this study was able to narrow the sociocultural and biological differences in the study population. In approximately half of the pairs, the patients were older than their sisters. Because of this distribution, birth order could be considered in comparing marital and reproductive histories of the patients and their sisters. As in previous investigations, fewer of the patients married than the sisters, and those who did were married at a later age, bore fewer children, and experienced a longer delay between marriage and first term pregnancy. These findings were independent of birth order.

The findings of this study are consistent with the current view that early marriage and reproductive history cause hormone changes which reduce the risks of future cancer of the breast. Also, they are consistent with the hypothesis that behavioral factors during adolescence or young adulthood may, in unknown ways, make early marriage and reproduction less desirable to women in whom breast cancer will develop later. Mechanisms for the latter hypothesis can only be speculated upon, but might be hormonal/genetic processes interacting with the cultural factors that influence marriage and reproductive practices.

As attitudes and practices relating to marriage and reproduction change, it may be increasingly difficult in the future to characterize the experiences of patients with cancer of the breast and their siblings. In order to carry out epidemiologic studies parallel to this one, it may be necessary to seek out unique groups whose lifestyles have remained relatively stable.

TABLE 4.—*Interval Between Marriage and First Term Pregnancy by Birth Order (both members married and had term pregnancies)*

	All Pairs		Patient Older		Patient Younger	
	Patients	Sisters	Patients	Sisters	Patients	Sisters
Mean (years)	3.0	1.8	2.2	1.8	3.8	1.8
No. of pairs ..	24		12		12	

TABLE 5.—*Term Pregnancies by Birth Order (both members married)*

	All Pairs		Patient Older		Patient Younger	
	Patients	Sisters	Patients	Sisters	Patients	Sisters
Mean	1.7	2.6	1.5	2.9	1.8	2.3
No. of pairs .	38		19		19	

TABLE 6.—*Pairs by Relative Number of Term Pregnancies and Birth Order (both members married)*

Relative Number of Term Pregnancies	All Pairs	Patient Older	Patient Younger
Patient had fewer .	24	14	10
Sister had fewer .	9	3	6
No difference	5	2	3
TOTAL	38	19	19

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Clinical and Virologic Course of Herpes Simplex Genitalis

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The clinical and virologic course of herpes simplex genitalis in women and men was examined in order to identify measurements useful in antiviral trials. Factors influencing the clinical course included initial disease versus recurrent disease, wet-skin versus dry-skin lesions, female versus male sex. Women with initial genital herpes had higher mean peak lesion virus titers than those with recurrent disease ($10^{4.5}$ pfu compared with $10^{2.5}$ pfu) and excreted virus longer (13 to 15 days compared with 6 to 8 days). Men with recurrent lesions had higher mean peak virus titers than women ($10^{4.0}$ pfu compared with $10^{2.5}$ pfu), but the duration of virus excretion was shorter (three to four days compared with six to eight days). There was pronounced variation in the clinical and virologic course of recurrent lesions among different patients and even within the same patient. These observations indicate several difficulties that must be considered in conducting careful antiviral trials in patients with herpes simplex genitalis.

GENITAL HERPES SIMPLEX VIRUS (HSV) infection is a commonly occurring venereal disease in the United States and in recent years has emerged as a public health problem of major proportions.[1] In the initial form of the disease, genital lesions can be painful and disabling; and complications such as urinary retention[2] and aseptic meningitis[3] may require admission to hospital. Recurrent disease is milder but may be associated with significant physical and psychologic morbidity. In pregnant women, active genital infection at the time of delivery can result in infection of the newborn infant during passage through the infected birth canal. In neonatal infection, mortality rates of 75 percent have been reported, with neurologic sequelae in most survivors.[4] Finally, HSV type 2 has been associated with and may have an etiologic role in carcinoma of the cervix.[5]

Because of the frequent occurrence and medical importance of genital HSV infections, many forms of therapy have been tried, including immunization with Bacillus Calmette-Guérin (BCG),[6,7] topical phototherapy with neutral red,[8-10] topical therapy with iododeoxyuridine alone,[11,12] iododeoxyuridine in dimethyl sulfoxide (DMSO),[13] or adenine arabinoside,[14,15] and systemic therapy with levamisole,[16] co-trimoxazole[17] or chlorpromazine.[18] With the possible exception of iododeoxyuridine in

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ABBREVIATIONS USED IN TEXT
DMSO = dimethyl sulfoxide
HSV = herpes simplex virus
pfu = plaque-forming units

DMSO,[13] none of these forms of therapy have proved effective in controlled clinical trials.

Several problems in the attempt to show antiviral efficacy are recognized, including the variable nature of the disease and the necessity of relying on subjective assessments to determine the effect of therapy. Our own studies[19] and those of others[9,12,14,15] indicate that lesion virology may provide a more accurate and objective assessment of disease severity. The purpose of this study was to define the clinical characteristics of herpes simplex genitalis lesions and to determine lesion virus titers in order to (1) identify those features of the disease that contribute to its variable course and (2) define more obective measurements of lesion severity for use in antiviral trials.

Patients and Methods

In May 1975, a clinic for the study of genital herpes was established in the clinical research center of the University of Utah Medical Center. In two years, 165 patients were referred for evaluation of which 130 were proved by viral isolation to have genital herpes, and 113 were included in the study. This group was then subdivided into women with initial disease (39 patients), women with recurrent disease (52 patients) and men with recurrent disease (22 patients). In women, initial disease was distinguished from recurrent disease by the absence of a history of previous disease and the presence of more severe and extensive lesions. Initial genital herpes in men was not observed. Referral was equally divided between private physician and public clinic sources.

Overall Study Design

At the initial interview, a complete history, physical examination and an informed consent were obtained. Women in whom the disease was occurring for the first time were evaluated by day 3 to 4 after the appearance of lesions. In all patients with a history of recurrent genital lesions, studies first were done to confirm HSV infection by virus isolation. Patients with proved herpetic disease were asked to return during the prodromal period or on the first day that lesions of their next episode appeared. All patients were requested to return for as many visits as possible during the observed episode. Of the total group of 113 patients with proved herpes genitalis, 72 patients appeared for one visit only, 17 patients had two visits, and 24 patients presented for three or more visits. Information gathered for each episode included a description of the prodrome, precipitating factors, location of lesions, and whether the episode was initial or recurrent. Information gathered for each daily visit included the number of lesions, stage of the lesions and the intensity of symptoms.

Lesion Evaluation

During all visits, lesions were classified into one of the following stages: no lesion (no physical evidence of a lesion but prodromal symptoms), vesicle, ulcer, crust or healed. Day 0 of the episode was defined as the day of physical onset of lesions. New lesions appearing at noncontiguous sites more than 24 hours after the eruption of the original lesions were followed as separate episodes. Pain was scored as objectively as possible using the following values: 1 = no pain, 2 = mild pain, 3 = moderate pain, 4 = severe pain.

Specimen Collection

A blood specimen was collected from every patient for syphilis serology (VDRL). A swab specimen was obtained from the cervix in women or urethra in men and streaked immediately onto Thayer-Martin medium for isolation of Neisseria gonorrhoeae. Specimens were processed by the routine diagnostic laboratories of the University of Utah Medical Center. In women with vaginitis, wet mounts and Gram stains of vaginal secretions were examined for the presence of Hemophilus vaginalis *clue* cells, Trichomonas vaginalis or Candida albicans. Papanicolaou smears were obtained for all women.

Dacron-tipped applicators were used to sample lesions for virus isolation and quantitation. When no lesion was present, the area indicated as tender by patients was abraded with a medium-moistened swab. Vesicles were unroofed and crusts removed before swabbing the lesion base. As much of the lesion area as possible was sampled. In women, after the lesions on the external genitalia were sampled, the labia were carefully and widely spread with fingers and a single sterile swab was passed through the introitus to sample both the vagina and cervix. A speculum was not used because pain was experienced by patients on introducing it into the vagina, and because passage of the speculum over introital lesions might result

in contamination of the vaginal walls and cervix. The swabs were immediately immersed in 1 ml of Eagle's minimal essential medium containing 50 μg per ml of gentamicin (Schering Corporation, Kenilworth, New Jersey), 10 μg per ml of amphotericin (Flow Laboratories, Rockville, Maryland) and 10 percent fetal bovine serum (Flow Laboratories). The specimens were frozen at −70°C within 30 minutes of collection.

Viral Assay

Virus was quantitated by the plaque titration method on fetal lamb kidney cells using techniques described previously.[19,20] Titers were expressed as total plaque-forming units (pfu) per specimen. First passage isolates of specimens were typed by a modification of the differential cytopathic effect technique described by Yang and co-workers[21] using chick embryo cells and fetal lamb kidney cells. Strains known to be type 1 or type 2 as determined by kinetic neutralization or immunofluorescence obtained from Dr. A. Nahmias (Emory University, Atlanta, Georgia) were included as controls.

Data Analysis

Data were programmed, stored and analyzed in the computers of the Department of Biophysics and Computing of the University of Utah College of Medicine. Only one *best* episode (most numbers of visits) was entered for each patient.

Results

Patient Population and Laboratory Data

At onset of disease, the mean age for women was 22 years and for men, 25 years (range 14 to 56 years). More than 95 percent of patients dated the onset of illness between 1972 and 1976. The mean age at first intercourse was 18 years in women and 15 years in men. The mean interval between first intercourse and the onset of genital herpes was four years in women and ten years in men. Approximately half of the patients had never been married, one quarter were married, and the remainder had been divorced one or more times. Of the women, 66 percent were using contraceptives, 10 percent had been sterilized and 24 percent used no contraceptive methods. Sixty-five percent of women and 80 percent of men had attended two or more years of college; some had pursued postgraduate studies. Marijuana was used more than once per week by 7 percent of patients. Only 4 percent of the patients reported periodic use of other common street drugs. However, most patients did admit to drug experimentation at least once in the past. None of the patients admitted to heavy alcohol consumption. None of the patients reported any significant medical or surgical illnesses, and none were taking any medication on a regular basis.

Findings on all physicial examinations made at time of first registering into the clinic were normal except for those in one man who was referred for evaluation of severe hypertension. Symptomatic vaginitis was noted in fewer than 10 percent of women; 40 percent of these were found to have either *clue* cells or trichomonads. Symptomatic moniliasis was unusual; only two women required treatment during the first two years of clinic operation. N. gonorrhoeae was not isolated from any of these patients. Four women had a positive VDRL; three of these were biologic false positive and one patient was subsequently treated for syphilis. Two patients were treated for condylomata accuminata and one for molluscum contagiosum. Cervical cytology showed some degree of inflammatory atypia in 19 percent of women and cells consistent with herpes infection in three women. No cervical lesions were observable in these latter three women. Two men described dysuria before and during a recurrence; results of routine and gonococcal cultures were negative.

Historical Data

A prodrome was noted by 46 percent of patients with recurrent disease. Characteristics of the prodrome were similar in women and men. Prodromal symptoms lasted more than 24 hours in 75 percent. Two thirds of those with prodromes had localized paresthesias consisting of itching, burning or a hypersensitivity of the skin surface at the site of the subsequent lesion. Prodromal neuralgia occurred in a quarter of patients, was always ipsilateral, and subsided shortly after the appearance of lesions. The buttock and groin were the most common sites of neuralgia but the thigh, calf, foot and scrotum were also involved. Two women noted unusual prodromes; one described a peculiar metallic taste in her mouth for several days before most recurrences and the other complained of pronounced irritability, lethargy and fatigue for 24 to 48 hours before the eruption of the lesions. Neither patient gave a history of oral herpes. Typical herpetic paresthesias and neuralgias were observed in two other women without any demonstrable lesions. These *false* prodromes usually occurred cyclically, often

in relation to the menses, and lasted 24 to 48 hours. Four women reported erythema multiformelike rashes that occurred periodically with recurrences.

Most women with recurrent disease (63 percent) did not identify a precipitating factor. Menses were related to the onset of an episode by 24 percent. A similar percentage of men (59 percent) did not identify a precipitating factor, but 32 percent related their episodes to intercourse.

There was little difference between men and women in the frequency or duration of recurrent lesions. Of the patients, 53 percent reported one or more recurrences per month; 33 percent reported recurrences every two to four months and 14 reported recurrences less frequently than every four months. Historically, the mean duration of recurrent episodes was seven days.

Clinical Observations

Dry-Skin Versus Wet-Skin Lesions. On dry skin surfaces, such as the labia majora, mons pubis, shaft of the penis, and thigh, individual lesions of both initial and recurrent disease in men and women were similar in appearance, duration and

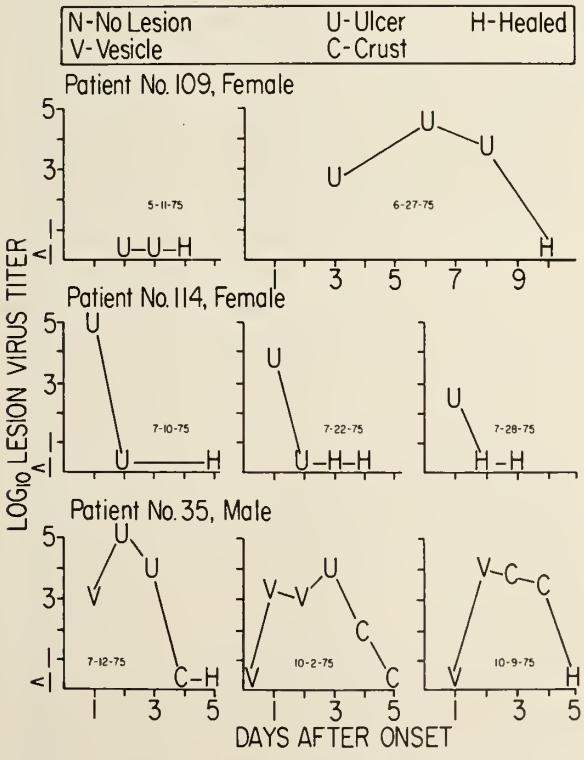

Figure 1.—Lesion stages and lesion virus titers in three patients with recurrent herpes simplex genitalis. The dates refer to the day of onset of each lesion.

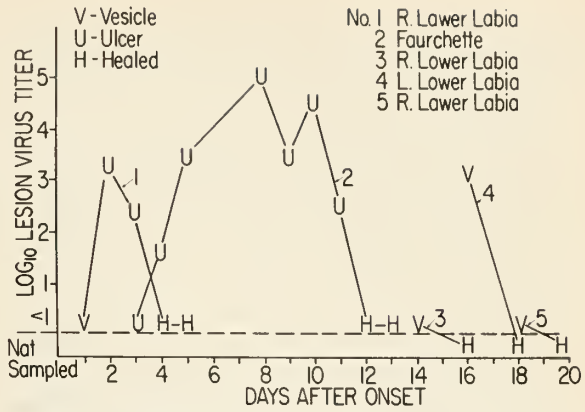

Figure 2.—Stages and virus titers of five separate lesions in a woman with recurrent disease over a 20-day period.

progression through the well-defined vesicular, ulcer, crust and healed stages that we observed in patients with recurrent herpes simplex labialis (Figure 1, Patient 35).[19] On dry skin, vesicles often persisted until the patient was seen. The ulcer stage was short, with a dry crust rapidly forming and reepithelialization progressing underneath the crust.

In chronically moist areas, such as the labia minora, introitus or fourchette in women and under the foreskin in uncircumcised men, lesion stages were not distinct because of maceration. The vesicular stage was rarely seen because vesicles quickly evolved into ulcers (Figure 1, Patients 109 and 114; Figure 2). Definite crusts were rarely seen. Instead, there was a gradual resolution of the inflammatory debris, with persistence of the ulcer and reepithelialization from the periphery of the lesion.

Initial Disease in Women. In women with initial disease, prodromal symptoms were unusual but, when present, consisted of paresthesias limited to the area where the disease would first erupt. Beginning at a localized focus, the vesiculo-ulcerative eruption spread in a wavelike fashion from the inital site across the external genitalia, thighs, buttocks, and frequently into the bladder, rectum and upper genital tract. Some lesions began healing while new ones erupted. In the moist skin areas, large, exquisitely tender ulcers formed with an erythematous, edematous base, giving the appearance of a second-degree burn. Systemic symptoms, described as *flu-like* with fever, headache, myalgia and abdominal pain, were present in 73 percent of patients. Four patients required admission to hospital: three for urinary retention and one for aseptic meningitis. Pain was severe.

The mean pain score (Figure 3) did not begin to decline until after day 9, and symptoms usually persisted for two weeks.

Recurrent Disease in Women. A third of women had only a single lesion; three quarters had no more than three lesions. The mean pain score was lower than in initial disease and declined to minimal levels by day 6 (Figure 4). Patients with multiple lesions had three patterns of lesion development: (1) A circumscribed, raised erythematous lesion formed with one or more vesicles or ulcers on its surface. The number of vesicles or ulcers was small—usually two or three, rarely as many as ten. Within the small anatomic area of recurrence, new vesicles would erupt while the initial ones were resolving. (2) A *cropping* pattern occurred in which the initial lesions resolved with complete healing of the skin. This was followed within hours to a few days by a second *crop* of lesions at the *same anatomic site* (Figure 1, Patient 114). (3) Less commonly, crops of lesions erupted at anatomically distinct sites around the external genitalia, the second crop beginning as the first was healing (Figure 2). For example, the anatomic areas could be mirror lesions of those on opposing labia, or they could be located at different sites on the same labia.

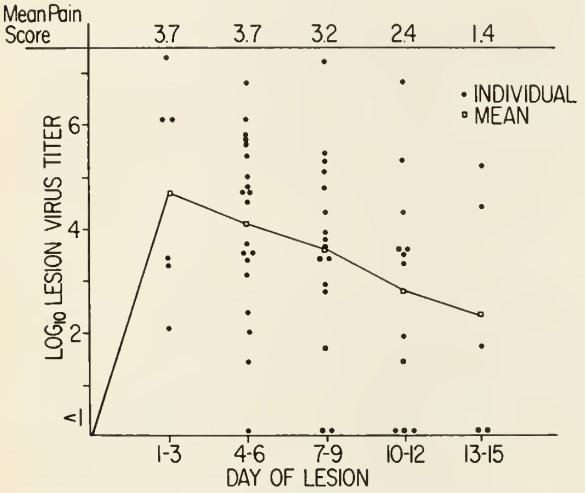

Figure 3.—Mean pain score and individual and mean lesion virus titers in 39 women with initial herpes simplex genitalis.

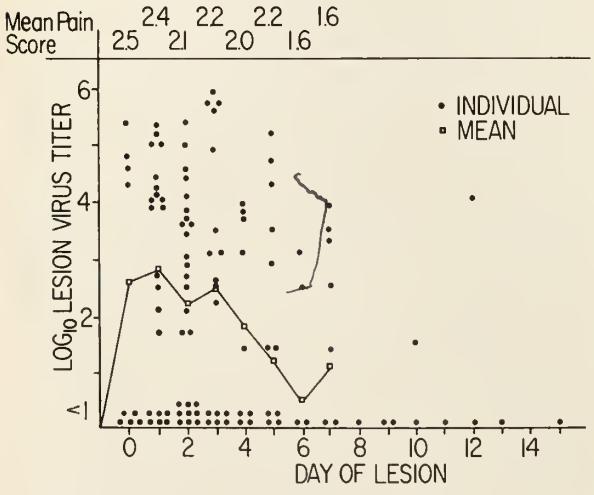

Figure 4.—Mean pain score and individual and mean lesion virus titers in 52 women with recurrent herpes simplex genitalis.

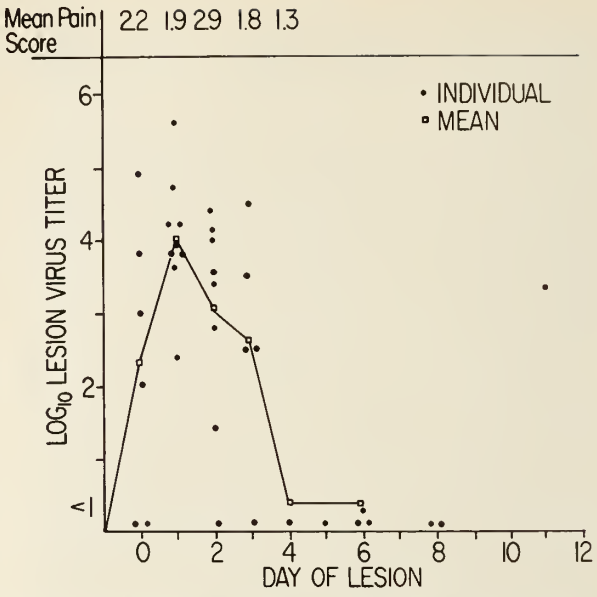

Figure 5.—Mean pain score and individual and mean lesion virus titers in 22 men with recurrent herpes simplex genitalis.

Some women with recurrent disease had ulcerations that were distinctly different from those that have been described previously.[22] Most common were linear ulcerations in the fourchette that superficially resembled inflamed excoriations. These occurred in 21 percent of women with recurrent disease and probably resulted from a combination of the tissue stresses peculiar to the fourchette and the continuous bathing of the area with purulent vaginal secretions. Less common was the herpetic chancre,[23] which was observed in two patients. These chancres were large, minimally tender ulcerations, up to 1 cm in diameter with sharply demarcated edges and a clean granular base. Results of darkfield examination and serologic testing for syphilis were negative. Herpes simplex virus was recovered from the herpetic chancre lesions in high titer.

Recurrent Disease in Men. Recurrent disease

in circumcised men followed a course similar to that described for recurrent herpes simplex labialis.[19] Fifty percent had no more than three lesions; 70 percent had no more than four lesions. The mean pain score through day 2 was similar to that in women with recurrent disease but declined to negligible levels by day 4 (Figure 5). Maceration of tissue was unusual unless the patient was not circumcised and the lesion was located under the foreskin.

Virologic Data

Individual and mean virus titers in 39 women with initial disease are shown in Figure 3. Only one patient was sampled on day 1 and few patients were seen before day 3. During the first three days, the mean virus titer was $10^{4.8}$ plaque-forming units (pfu) and virus was recovered from all specimens. Thereafter, titers declined in a linear fashion. A progressive increase in the number of virus-negative samples was not observed, since patients with healing lesions did not, as a rule, return for follow-up examinations. The patients who did return after day 9 were more likely to have symptomatic, virus-positive lesions. It is probable, therefore, that the mean virus titer for the entire group of 39 patients declined more rapidly than is indicated in Figure 3.

The titers of virus in women with recurrent herpes genitalis are shown in Figure 4. In contrast to the titers in initial disease, mean peak virus titers were in the $10^{2.5}$ to $10^{2.8}$ pfu range during the first three days of the illness, primarily because there were more patients with virus-negative lesions. Mean titers rapidly declined after day 3, although a number of patients continued to have virus-positive lesions. Only one of the 52 patients had virus isolated after day 7, the positive specimens indicated in Figure 4 on day 10 and day 12.

Virus titers in men with recurrent disease are illustrated in Figure 5. Virus titers increased from a mean of $10^{2.3}$ pfu on day 0 to $10^{4.0}$ pfu on day 1 but declined rapidly thereafter. Only one of the 22 patients had virus recovered from a lesion after day 3.

Pronounced variability in clinical staging of the lesion, virus titers and duration of virus excretion was noted among different patients and even between separate episodes in the same patient. Figure 2 illustrates the course of five separate and distinct recurrent lesions that occurred on the external genitalia of a woman over a 20-day period. The clinical and virologic evolution of each lesion was quite different. A vesicle was the initial stage in four of the lesions; virus was isolated from vesicle fluid in only one of these. Duration of the individual lesions varied from two to ten days and peak virus titers ranged from undetectable to $10^{5.0}$ pfu. In Figure 1 the clinical and virologic courses of eight separate episodes of recurrent herpes simplex genitalis in three different patients are illustrated. In one woman, patient 109, no virus was isolated in the first observed recurrent episode, while appreciable titers were recovered for six days during another episode six weeks later. Patient 114, a woman, had three separate and distinct episodes separated by only a few days. Although the patterns of virus excretion were similar for the episodes, the maximum virus titers were quite different. In patient 35, a man, the duration of virus excretion and peak virus titers from three separate episodes were quite similar.

One hundred isolates were typed: 81 percent were type 2 and the remainder type 1. Because of the small number of type 1 isolates, no attempt was made to distinguish differences in the clinical or virologic courses of illness due to the two serotypes. Both cervical/vaginal and external genital specimens were obtained from 93 recurrences in 52 women. Eighteen (19 percent) of the cervical/vaginal samples were positive in patients where the concomitant vulvar specimen also showed virus. Of the 18 positive cervical/vaginal isolates, 17 were type 2 and one was type 1.

Comment

Previous studies of herpes simplex genitalis have indicated that patients are largely from a lower socioeconomic group,[24] and have a high incidence of other types of venereal disease, particularly gonorrhea.[25-28] Most patients in this study were well educated and appeared to be from middle and upper socioeconomic groups. No cases of gonorrhea and only one case of syphilis were observed. Although our subjects with genital herpes may reflect the predominantly middle-class background of Salt Lake City, the patients with gonorrhea seen at our medical center are largely from a lower socioeconomic group. Our observations are consistent with those of Gardner and Kaufman,[29] which indicate that genital herpes is more of a problem than gonorrhea in patients of a private gynecologic practice. It may be that private patients with gonorrhea are not referred

to a medical center since the disease can be diagnosed and treated easily in an office setting, while patients with genital herpes are referred because methods for accurate diagnosis are not widely available and there is no effective therapy.

Moist-skin lesions (on labia minora, introitus and fourchette in women and under the foreskin in men) healed slowly from the periphery of the lesion and appeared to last longer than dry-skin lesions. The dry-skin lesions (on labia majora, mons pubis, shaft of the penis, skin of thigh, and the like), on the other hand, evolved rapidly through well-defined vesicle, ulcer and crust stages with healing progressing underneath the crust. The healed stage in moist lesions was more difficult to define because there was gradual disappearance of the lesion, while in dry lesions healing was usually heralded by loss of crust, an easily discernible event. Recurrent lesions in women appeared to be symptomatic longer than those in men (appreciable pain for six to eight days compared with three to four days) and to excrete virus longer (six to eight days compared with three to four days), perhaps because moist-skin lesions were more prevalent in women.

Women with initial genital herpes had lesion virus titers that were much higher than titers in those with recurrent disease during the early phase of illness (mean titers approximately $10^{4.5}$ pfu compared with $10^{2.5}$ pfu), had fewer virus-negative specimens (Figures 3 and 4) and excreted virus longer (13 to 15 days compared with 6 to 8 days). Quantitative lesion virology in women with genital herpes has not been previously reported, but other studies have noted duration of virus excretion similar to our observation.[9,13,15,34] Men with recurrent lesions had higher peak virus titers than women (mean $10^{4.0}$ pfu compared with $10^{2.5}$ pfu), but the duration of viral excretion was shorter (three to four days compared with six to eight days). Our virus titer results in men are similar to those observed by Goodman and co-workers.[14]

One of the most significant observations in our study is the notable variation in the clinical and virologic course of recurrences between different patients and even within the same patient. Figures 4 and 5 show the considerable scatter in virus titers from different patients on the same day of an episode. Figure 2 illustrates five separate crops of lesions that occurred at different anatomical sites in the same patient over a 20-day period. If this one patient had not been examined carefully and followed frequently, the recurrences might have been considered a single prolonged lesion with peak virus excretion on day 8 and lasting 20 days, rather than five separate lesions. Figure 1 illustrates the different clinical and virologic pattern not only between patients but also within the same patient. The lesions in these three patients recurred at the same anatomic site with a variable disease-free interval in between. From these data, the question of what reasonably constitutes a separate and distinct recurrent episode can be raised. More patients need to be examined and evaluated carefully to provide a definitive answer to this question.

There are many implications for antiviral clinical trials from the results in this study: (1) In many instances, and particularly with the dry-skin lesions, it is apparent that the natural healing process may begin within the first day or two after the onset of the episode. Topical antiviral therapy, therefore, must be applied as soon as possible after onset of a recurrence, preferably within 24 hours, in order to allow maximal opportunity for the compound to work. The fact that 46 percent of the patients have prodromal symptoms would be an aid in this regard. (2) The pronounced variability in the clinical and virologic course of recurrences between different patients dictates that a large number of patients be studied in order to identify any true differences due to drugs. (3) Because the character of recurrences in men differs appreciably from that in women, drug-placebo randomization and data analysis should be done separately by sex. (4) Because the clinical and virologic course of dry-skin lesions differs from that of wet-skin lesions, it may be that the results of treatment of these different types of lesions will have to be analyzed separately. (5) Since there is variation in severity of recurrences even within the same patient, previous episodes in the same patient cannot be used as a control. (6) The phenomenon of successive, separate crops of lesions at the same site or different anatomic sites in the same patient creates problems in the interpretation of data related to the reduction of severity of the episodes. For example, if only the site of the initially apparent lesion was treated (as was done with several of the trials of neutral red phototherapy), the appearance of new lesions at new untreated sites could be erroneously interpreted as drug failure. In addition, the appearance of new lesions at the same site that had received a course of topical therapy several days previously

could be interpreted as drug failure. The newly appearing lesions could be the result of additional virus from sacral ganglia rather than inability of the drug to inhibit replication of virus in the skin. (7) If frequency of recurrences is evaluated as a measure of antiviral efficacy, the definition of what constitutes a separate recurrence will need to be clarified, as mentioned above. (8) The definition of healing in moist-skin lesions may be difficult, since the ulcer slowly resolves by reepithelialization from the periphery. Lesion healing, since it may occur from one to two weeks after onset, is usually determined privately by the patient rather than during return clinic visits for evaluation by independent observers. In women, self-visualization of genital lesions is difficult, and the moist-skin lesions are more prevalent in women. The result may be unavoidable inaccuracies in determination of the endpoint of lesion healing. This is an unfortunate likelihood, since time to complete healing was the most sensitive clinical measurement evaluated in distinguishng between lesions of differing severity in patients with recurrent herpes labialis.[19] (9) As indicated by our data and the data of others,[22,26] the measurement of lesion healing may not be a valid assessment of *antiviral efficacy* in moist-skin lesions, since tissue maceration is common in these areas. (10) Finally, the data suggest that objective and quantitative measures such as lesion virus titers and duration of lesion virus excretion will be valuable in the attempt to assess antiviral efficacy.

The results of this study indicate that a carefully executed, adequately controlled clinical trial in patients with recurrent herpes simplex genitalis will not be an easy task. We were not so successful as we had hoped in getting patients to return for frequent and regular clinic visits, a problem noted in other studies of herpes simplex genitalis.[9,12,15] Such frequency and regular visits will be necessary in order to define precisely the duration of the various lesion stages, the time to complete healing, serial virus titers, "area under the virus titer curve" (titer hour-area), duration of virus excretion and other measurements that we were able to quantitate in patients with recurrent herpes simplex labialis.[19] We are attempting to conduct such a study at present. With the recent availablity of several promising antiviral compounds for the treatment of herpes simplex virus infections,[30,31] it is realistic to hope for successful therapy in the not-too-distant future. Detailed information concerning the natural history of herpes genitalis is a necessary step in the proper design of clinical trials.

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Specialty Conference

Refer to: Longmire WP Jr, Goldstein LI, Sample WF, et al: The treatment of retained gallstones—Interdepartmental Clinical Conference, UCLA School of Medicine (Specialty Conference). West J Med 130:422-434, May 1979

Moderator

WILLIAM P. LONGMIRE, JR., MD

Discussants

LEONARD I. GOLDSTEIN, MD
WILLIAM FREDERICK SAMPLE, MD
BARBARA KADELL, MD
RONALD K. TOMPKINS, MD

An edited transcription of an Interdepartmental Clinical Case Conference arranged by the Department of Medicine of the UCLA School of Medicine (University of California, Los Angeles).

The Treatment of Retained Gallstones

Various techniques are available to evaluate patients suspected of having common duct stones before an operation on the biliary tract. In patients without jaundice, intravenous cholangiography with tomography may provide satisfactory visualization of the biliary system and its contents. Sonography and computerized axial tomography are useful noninvasive methods. Endoscopic retrograde and transhepatic cholangiography are invasive techniques; but, when successful, they provide the most precise preoperative information obtainable about the presence or absence of stones in the biliary system. The most appropriate diagnostic procedures must be carefully selected for each patient. Each year in 3,000 to 4,000 cases, stones are found remaining in the bile ducts after common duct exploration for the removal of stones. Retained stones can be treated by nonoperative extraction, by irrigation techniques and by surgical removal. Extraction methods probably deserve first consideration, if experienced personnel are available. The technique of irrigation of the common bile duct with cholic acid or other solutions, although limited in success, may also be tried; if these procedures fail, then reoperation is indicated.

WILLIAM P. LONGMIRE, JR., MD:* *Despite the best efforts of surgeons to remove all stones from the biliary tract of patients with choledocholithiasis, published reports indicate that one or more stones will be left behind in 5 percent to 9 percent of patients in whom common duct exploration is done. In a 1957 review of such cases from the* UCLA, *Harbor General and Wadsworth hospitals, Smith*[1] *noted that the common bile duct was explored in 16 percent of patients in whom cholecystectomy was carried out. Retained common duct stones were subsequently diagnosed in*

*Department of Surgery, UCLA School of Medicine.

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ABBREVIATIONS USED IN TEXT

CDC = chenodeoxycholic acid
ERCP = endoscopic retrograde cholangiopancreatography
THC = transhepatic cholangiography

6.6 percent of those in whom the common bile duct was explored. Retained stones were not found in any patient in whom the exploration had been negative; all overlooked stones occurred in patients who had had multiple stones removed.

It is important to differentiate between recurrent stones and retained stones. Once the gallbladder (the original site of formation of most common duct stones) has been removed, the de novo *formation of stones in patients who live in North America is unusual. Such "primary" stones consist of soft pigment, are lacking in cholesterol and calcium and almost invariably are associated with some structural or physiological abnormality of the ductal system. In the United States, cholecystectomy is the most common abdominal operation; approximately 3,000 to 4,000 patients each year are unfortunate enough to have retained stones in the common bile duct after cholecystectomy.*

The problem is not new. More than 70 years ago William Halsted,[2] who performed one of the earliest operations on the gallbladder, stated that a reliable, simple method was needed to determine accurately the presence of stones in the common bile duct. Twenty years later Dr. Halsted was himself to die of complications after the removal of a retained common duct stone.

In this conference our panel members will discuss (1) methods of diagnosing stones in the common bile duct; (2) methods of treating these stones; (3) the surgical removal of stones from the common bile duct; and finally (4) the methods that are being used today to decrease the prevalence of this condition.*

Our first two presentations will focus on the diagnosis of stones in the common bile duct.

For several years percutaneous transhepatic cholangiography has been the most definitive diagnostic technique available to diagnose extrahepatic biliary obstruction. It has two disadvantages: nonvisualization of the ductal system and postoperative cholangiographic complications. However, these have been minimized by recent improvements of the technique, which Dr. Goldstein will discuss. He will also comment on the contributions of endoscopic retrograde cholangiopancreatography to the diagnosis of extrahepatic biliary obstruction.

*Although not discussed in this conference, retained stones in poor-risk patients have also been removed by endoscopic papillotomy. At present this procedure is being done in a limited number of centers in this country. It has been more widely used in Europe but must still be considered as a procedure under evaluation. In the group of poor-risk patients on whom the procedure has been done in this country, serious complications and deaths have occurred.

Invasive Diagnostic Procedures

LEONARD I. GOLDSTEIN, MD:† The preoperative assessment of a patient with retained common duct stone may present a problem in differentiating medical jaundice from surgical jaundice. Historical information, physical examination and routine biochemical liver tests can only suggest the correct diagnosis in most patients.[3] Tests such as liver biopsy, isotopic scanning and hypotonic duodenography may not necessarily be helpful in making this separation and could be hazardous.[4] Only direct radiologic visualization of the biliary tree offers definitive diagnostic information. (Gray scale ultrasonography, which will be discussed subsequently by Dr. Sample, may offer a noninvasive alternative method of assessing this problem.)

Two methods for visualizing the biliary ducts are currently used in the United States, after being first developed in Japan in the early 1970's. Although endoscopic retrograde cholangiopancreatography (ERCP) is a low risk technique, it is difficult to perform. A survey of experience with ERCP in the United States showed that the total cannulation success rate was 70 percent; total complication rate, including predominantly pancreatitis, cholangitis and drug reactions, was 3 percent; and death rate was 0.2 percent.[5] At UCLA we have limited experience with this technique, mainly because of the technical difficulties, and have preferred to use transhepatic cholangiography (THC).

Complications of THC in the past had discouraged the use of this procedure. Okuda and colleagues,[6] however, have modified this technique to the extent that it has now repeatedly been shown to be safe, accurate and extremely valuable.[7,8] The modifications include (1) the use of a flexible steel needle approximately 15 to 17 cm long, 0.7 mm external diameter and 0.5 mm internal diameter, commonly called the thin or

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TABLE 1.—*Thin Needle Cholangiography in 50 Patients**

Biliary Duct	Number of Patients	Visualization		Complication	
		Number	Percent	Number	Percent
Obstructed	29	29/29	100	2/29	6.9
Nonobstructed	21	12/21	55	0/21	0
TOTAL		41/50	82	2/50	4

*Data from Goldstein et al.[9]

skinny needle; (2) entry from the lateral chest wall, which provides better protection against bile leakage because of the thickness of the liver tissue through which the needle passes; and (3) fluoroscopic monitoring.

Procedure

At UCLA, THC is done in the radiology department. The skinny needle is inserted into the liver from a right lateral approach toward the junction of the common hepatic ducts. Contrast material is injected slowly with only minimal pressure while the needle is withdrawn. When an intrahepatic bile duct is seen, an attempt to aspirate bile from the biliary duct system is made. This may be done easily if the needle is in a large bile radicle; aspiration from a small peripheral bile radicle is often unsuccessful. The aspiration of bile clearly reduces the incidence of complications, particularly cholangiovenous sepsis.[6] If on withdrawing the needle from the hepatic tissue no bile duct has been entered, the needle is removed and another entry is made at the same cutaneous site. With dilated bile ducts, the biliary system is often seen on the first attempt. After five attempts, failure to see the bile ducts virtually excludes biliary obstruction. Other hepatic structures are entered and are easily recognized by the flow pattern of the injected contrast material.

Most observers report a success rate of 100 percent in patients with obstructed ducts and about 60 percent visualization of normal ducts. Our experience with this procedure (Table 1)[9] has been in agreement with the other reported series. In two of our 29 patients with obstructed ducts, fever and positive blood cultures developed one to three hours after this procedure. Both responded rapidly to conventional antibiotic therapy without any of the serious circulatory events often associated with cholangitis. Surgery was done in both patients according to elective scheduling. In no patient subsequently operated on was there any evidence of bile leakage or intraperitoneal hemorrhage. Because the frequency of reported complications (bile leak, hemorrhage and exacerbation of sepsis) is so low, laparotomy need not be routinely scheduled to follow this procedure.

Endoscopic retrograde cholangiopancreatography and THC are complementary procedures of great value in the patient with jaundice.[10] By providing accurate diagnosis, these techniques have virtually eliminated the potential hazard of operation on a patient with a medical disorder simulating surgical obstruction. Figures 1 to 3 illustrate the use of transhepatic cholangiography in the assessment of patients with jaundice.

DR. LONGMIRE: *The continued improvements and refinements in ultrasonography have provided another excellent noninvasive differential diagnostic technique for obstructive jaundice. Not only have techniques been improved but experience in interpretation has also played a role in improving the effectiveness of the procedure. Dr. Sample, who has been involved in these studies almost since their inception, will comment on the value*

Figure 1.—Normal transhepatic cholangiogram in a patient with previous cholecystectomy.

as well as on the limitations of ultrasonography. The staff at the UCLA *Hospital, like so many others in the country, is evaluating the diagnostic potential of the total body scanner for various conditions. Dr. Sample will speak on the current expectations of this modality.*

Noninvasive Techniques for the Diagnosis of Retained Gallstones

WILLIAM FREDERICK SAMPLE, MD:* A technological revolution is occurring in the diagnostic imaging fields; it has resulted from the sudden merger of recent advances in electronics, signal processing, computer sciences and mathematics. The development of reconstructive imaging capabilities has led to two new important noninvasive diagnostic modalities: gray scale ultrasound and computed tomographc body scanning. Both noninvasive diagnostic procedures hold great promise in evaluation of patients with biliary tract disease in that they are not limited by physiological effects of biliary obstruction.

Ultrasound uses the reflections of high-frequency sound waves from within the body for image reconstruction. With the recent advances in gray scale signal processing, as well as the improved focusing of the sound beam, an incredible degree of resolution has been achieved in the high retroperitoneum and upper abdomen.[11-15] The glandular elements of the liver, spleen, pancreas, kidneys and adrenal glands can now be seen in a high percentage of patients. In addition, the gallbladder can usually be seen in a fasting patient, as can the common duct in a significant percentage of normal patients. The intrahepatic biliary radicals are not normally resolved. Several vascular structures, which represent important boundary landmarks for the various organs, can routinely be seen. These include the hepatic and portal venous systems, the inferior vena cava, the superior mesenteric vein, the aorta, the superior mesenteric artery, the celiac artery, the splenic artery, the hepatic artery and the gastroduodenal artery.

Greater accuracy in the differential diagnosis of upper abdominal diseases has been obtained as a result of improved resolution.[16,17] In biliary tract disease, ultrasonic examination has been shown to be an effective supplement to the nonvisualizing oral cholecystogram.[18] Most of the recent series have shown ultrasonography to be superior to double-dose oral cholecystography and intravenous cholangiography for the differentiation between normal and abnormal biliary tracts.[19] Biliary stones as small as 2 or 3 mm in diameter can be seen, and calcification is not necessary for visualization.

In the evaluation of jaundice, conventional noninvasive techniques, such as intravenous cholangiography, may not be possible. Furthermore,

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Figure 2.—Right, Transhepatic cholangiogram showing dilated common duct caused by impacted stone in a patient two years after cholecystectomy. **Left,** Typical "meniscus signs" **(arrows)** caused by impacted stones.

rose bengal nuclear scanning has been more time consuming and has only occasionally proved diagnostic.[20] During the postoperative period, when a T-tube is often available, T-tube cholangiography is the diagnostic procedure of choice.

The initial evaluations of ultrasound in the differential diagnosis of medical jaundice and surgical jaundice have been encouraging.[21-23] By visualizing dilated intrahepatic biliary radicals or a dilated common bile duct, an accuracy of more than 90 percent in the detection of obstructive jaundice has been reported for most series. In our experience with 35 patients diagnosed by immediate transhepatic cholangiography, only two of the 35 ultrasonic evaluations were found to be technically suboptimal.[24] In the remaining 33 patients, ultrasound examination correctly distinguished obstructive jaundice from medical jaundice.

Figure 3.—Transhepatic cholangiogram showing numerous ductal stones in a patient with painless jaundice.

In some cases of biliary obstruction, the site and cause of the obstruction can be shown by gray scale ultrasound. Calcified common duct stones can be recognized by their shadowing effect, whereas noncalcified stones appear in the common bile duct as reflective structures without shadowing (Figure 4A). Abnormalities can frequently be detected (Figure 4B) in pancreatic texture related to tumor or pancreatitis.

The advantages of ultrasound examination include the absence of toxicity, the inherent flexibility, the rapidity with which the study can be done and the relatively low cost. The major limitations include the long training necessary to perform the scans as well as to interpret them, the high degree of dependence on operator skill with the present instrumentation, and in some patients gas-containing bowel patterns that prevent visualization.

With computed tomography, the differential attenuation of x-rays is monitored and reconstructively imaged. With present equipment, spatial resolution of 1 to 2 mm and contrast resolution of 0.5 percent are possible.

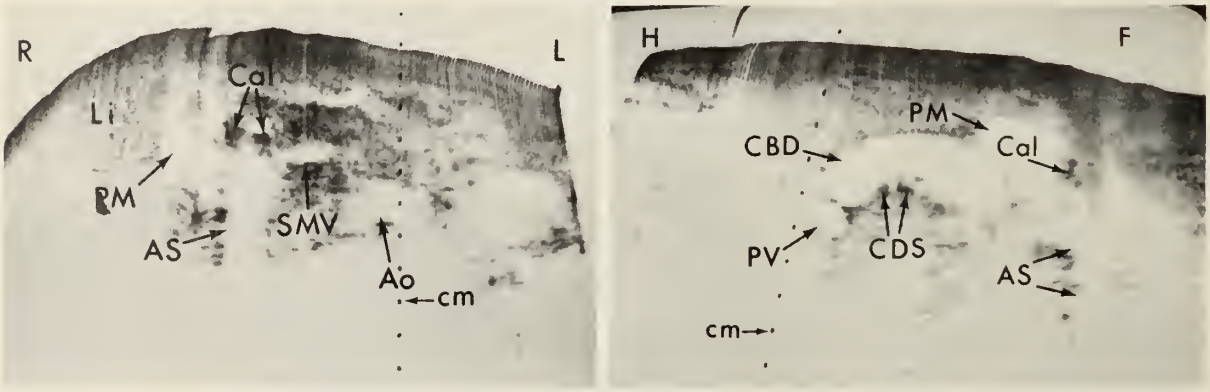

Figure 4.—Gray scale sonogram. **Right,** Longitudinal to the right of the midline showing a dilated common bile duct (CBD) anterior to the portal vein (PV) and containing some highly reflective material that does not shadow the sound representing noncalcified common duct stones (CDS). A mass is present in the head of the pancreas (PM), which contains highly reflective calcifications (Cal) showing acoustical shadowing (AS). H = head, F = feet; and cm = centimeter marker. **Left,** Transverse through the head of the pancreas showing a pancreatic mass (PM) containing calcifications (Cal), which show acoustical shadowing (AS) proved at surgery to be chronic pancreatitis. Li = liver, SMV = superior mesenteric vein, Ao = aorta, R = right side, L = left side and cm = centimeter marker.

The importance of computerized tomography in the evaluation of neurological patients is well established.[25] The application of the same reconstructive imaging principles to the rest of the body has been somewhat more difficult for several reasons: a larger area is examined, the natural symmetry in the intracranial portions of the body does not exist, and the inherent contrast provided by the blood brain barrier is absent. Nevertheless, the initial evaluations of computerized reconstructive techniques for the abdominal region have been encouraging.[26-28] To see the various organs within the upper abdomen, a certain degree of retroperitoneal fat is required to act as a natural contrast agent. In this situation, the liver, spleen, pancreas, kidneys, adrenals and much of the abdominal vasculature can be seen. The gallbladder can usually be detected; however, the normal common duct is not usually seen without intravenous administration of contrast agents.

Although computerized tomographic imaging of the body is in its infancy, evaluation of biliary disease is readily possible with this noninvasive technique. The mass effect of pancreatic inflammation or neoplasia can be detected (Figure 5A) and the dilated common bile ducts and intrahepatic biliary radicals can be seen (Figure 5B). The technique is particularly sensitive to calcified stones within the biliary system. The thickness of the tomographic section (13 mm), however, has made small noncalcified common duct stones difficult to image because of a partial volume phenomenon.

The advantage of computerized tomography is the technical ease of obtaining the images with less dependence on operator skill and a more rapid adaptation to the transverse tomographic anatomy related to the fact that a complete cross section of the body is obtained. The relative disadvantages are the additional radiation exposure, the cost of the instrumentation, the inflexibility of only one tomographic plane, and the frequent need for the addition of orally and intravenously administered contrast agents.

We do not believe that gray scale ultrasound or computerized body scanning will replace the better established conventional means of evaluating the biliary tract, that is, T-tube cholangiography and transhepatic cholangiography. For those patients in whom noninvasive conventional techniques have failed, both gray scale ultrasound and computerized body scanning hold great promise. At present, the limitations of each modality are offset by the strengths of the other. During the next few years, the exact position of each technique will be established in the sequential diagnostic approach to patients with biliary tract disease. At UCLA, ultrasonography is used as the first diagnostic modality in cases of nonvisualized oral cholecystograms and in patients with jaundice. If results from this examination are technically unsatisfactory, then the computerized body scanning techniques are applied. Usually, one of these modalities will suggest which of the following invasive techniques should be used: immediate operation, transhepatic cholangiography, endoscopic retrograde cholangiopancreatography or needle liver biopsy.

DR. LONGMIRE: *With a disease as common as*

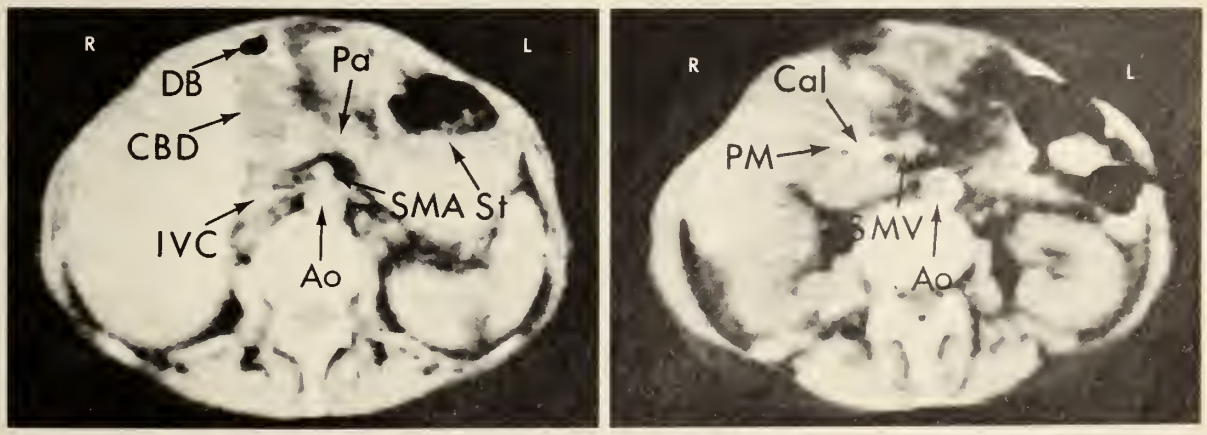

Figure 5.—Transverse computed tomograms. **Right,** At the level of the head of the pancreas showing a pancreatic mass (PM) containing calcifications (Cal), which at surgery proved to be chronic pancreatitis. SMV = superior mesenteric vein, Ao = aorta, R = right side and L = left side. **Left,** 2 cm above first level showing a dilated common bile duct (CBD). DB = duodenal bulb, Pa = pancreas, IVC = inferior vena cava, Ao = aorta, SMA = superior mesenteric artery, St = stomach, R = right side and L = left side.

gallstones, there would be great interest in any new treatment designed to eliminate the need for operative removal. Most of the recent studies involve the use of chemical preparations to dissolve stones in the gallbladder. Efforts to eradicate stones on the ductal system have been limited; but, with experience and with development of improved medical therapy of cholelithiasis, it may become possible to treat both ductal and gallbladder stones by chemical methods. Dr. Goldstein will comment on the current status of this therapy.

Medical Therapy of Retained Gallstones

DR. GOLDSTEIN: Despite intensive surgical efforts for detecting ductal stones and despite routine use of operative cholangiography, retained common duct stones still occur in about 10 percent of patients in whom surgical operations were done on the gallbladder.[29] When a stone is discovered, usually by postoperative T-tube cholangiography or because of symptoms related to T-tube drainage or clampage, the surgeon is faced with few choices.[30] Residual calculi that obstruct the common duct and prevent the flow of bile into the duodenum must be removed. Calculi appearing free within the ductal system should also be removed; however, this is not mandatory because the degree and extent of future obstruction is unpredictable.[31] Way and Motson[32] have suggested that no treatment be attempted for four to six weeks after initial surgical operation, since about 10 percent to 20 percent of stones found on early x-ray films (particularly those less than 0.5 cm in diameter) may pass spontaneously into the duodenum, thus requiring no further treatment. Retained stones that are left untreated may eventually produce serious complications. Because early reoperation is especially hazardous,[33] several nonsurgical approaches to therapy of the retained stone have been developed. This medical therapy depends specifically on type of stone and consists mainly of attempts at flushing, pharmacologic relaxation of the sphincter of Oddi and dissolution or fragmentation or both with cholesterol solvents.[32] As early as 1891, Walker[34] reported success in dissolving an impacted cystic duct stone by injecting ether through a cholecystectomy sinus tract. Subsequently, ether or chloroform was used. Numerous potential pitfalls and dangers are associated with the use of these solvents, and they are no longer commonly used.[32] Since the 1890's, various infusions have been recommended in which (singly or in combination) antispasmodics, topic anesthetics or simple flushing solutions were used through the T-tube. The two most popular regimens for the dissolution (fragmentation) of cholesterol stones have been bile salt solutions and heparin.

Heparin

Gardner and his colleagues[35] reported success in 31 of 43 patients with retained stones treated with infusion of heparinized saline. Their regimen consisted in infusion of 250 ml of 0.15 N sodium chloride solution containing 25,000 units of heparin every eight hours as a continuous drip until the stone disappeared. Gardner acknowledges that the exact mechanism of action of heparin is not known; fragmentation seems most likely. Heparin may affect the stone surface directly, specifically the mucopolysaccharides within the gallstones.[36] Other workers, however, have failed to confirm the efficacy of heparin either *in vitro* or *in vivo*.

Bile Acid Perfusion

The T-tube infusion of sodium cholate is a method currently used and may be of some value.[30,37] Sodium cholate promotes the dissolution of gallstones by its effects on micellar solubilization of lipid, with reduction in size of the stone or possible fragmentation or both. Sodium cholate, 200 mM in 0.15 N sodium chloride solution buffered to pH 7.5 and prefiltered through a 0.22 μ millipore filter, is infused continuously at a rate of 30 ml per hour with continuous monitoring of intrabiliary pressure through a T-tube.[32] Reported complications of sodium cholate infusion include diarrhea, impaction of a gallstone at the ampulla of Vater, pancreatitis and cholangitis.[38] Diarrhea, the most distressing side effect, may be prevented by administration of cholestyramine, a bile acid binding resin. Cholangitis may be related to the abrupt increase in the biliary pressure. Way and associates[30] originally reported successful dissolution in 12 of 22 patients with response occurring within the first few weeks of treatment. The current experience of Way and Motson[32] includes successful dissolution in 33 of 49 additional patients (67 percent); treatment was not continued after 14 days. Lansford and colleagues[37] reported success in five of six patients within five days after beginning treatment with sodium cholate; both of these studies were uncontrolled. Results of a controlled trial from the Mayo Clinic[39] are not encouraging. In this study, patients received sequentially four-day infusions

with 75 mM sodium cholate and 150 mM sodium chloride at 30 ml per hour in randomized order. During infusion with cholate solution, stones disappeared in two of the six patients; saline infusion produced no effect. This low success rate was associated with a high incidence of side effects. With this experimental evidence,[40] it seems highly unlikely that the bile salt infusions would have sufficient time to dissolve retained stones completely; more likely the stones become smaller and thereby pass easily into the duodenum. Although other bile salts and certain quatenary ammonium detergents have been used *in vitro*,[41] the lack of animal testing prohibits their administration in humans.

Finally, d-limonene, a terpene organic solvent similar to ether and chloroform, has been found by Japanese investigators to be highly efficacious in the management of retained duct stone. In 13 of 15 patients there was successful dissolution of gallstones with this agent without significant side effects.[42]

All these agents have had limited success in the dissolution of cholesterol gallstones. Although pigment stones are not affected by these measures, they may be susceptible to being dissolved.[43]

Medical Therapy

Research advances in the pathogenesis of cholesterol gallstones have placed us on the threshold of a new era in the treatment of gallstone disease. Chenodeoxycholic acid (CDC), a primary bile acid, has repeatedly been shown to be efficacious in the treatment of cholesterol gallstone disease. In asymptomatic patients with radiologically visualized gallbladders treated with 750 mg to 1 gram of CDC for one to three years, gallstone dissolution will occur in 50 percent or more.[44] Chenotherapy expands the bile acid pool, decreases hepatic cholesterol synthesis, decreases cholesterol secretion into the bile, and thereby promotes the desaturation of the biliary lipid and the dissolution of stones.[45]

Limited experience with CDC for choledocholithiasis may be found in some of the larger series. Dowling[46] treated five patients with duct stones and noted possible disappearance of stones in one patient based on the improvement in symptoms of cholangitis. Thistle and co-workers[47] reported that in 11 patients with biliary duct stones, response (not defined) occurred in five patients observed for 6 to 24 months. Barbara and colleagues[48] have recently reported that of eight patients with choledocholithiasis treated with CDC (dosage varying between 2 mg and 15 mg per kg of body weight once a day for five months) complete dissolution occurred in three patients, and partial dissolution in two.

Another agent of potential efficacy in the treatment of retained stone is Zanchol, a synthetic fluoranthrene derivative with known choleretic properties.[49] Zanchol reduces the cholesterol concentration of bile, and it may prove to be of some value as a litholytic agent.

DR. LONGMIRE: *The technique of nonoperative extraction of retained stones, first described by Mondet[50]* in 1962, has been extensively pursued and developed in several medical centers. Mazzariello[51] in Argentina reported on a personal series of more than 500 cases. Burhenne[52] in San Francisco, with a personal series of more than 300 cases, published a cooperative study of 38 hospitals involving more than 600 extraction procedures. Dr. Kadell will comment on this technique.*

Nonoperative Extraction of Retained Common Duct Stones

BARBARA KADELL, MD:† The concept of a nonoperative method for removing retained biliary stones, using the T-tube tract as a point of entry into the bile ducts, is not new.[51,53,54] However, only since 1973 when Burhenne[55] (Children's Hospital, San Francisco) described his technique and ingenious instrumentation has the procedure become the important therapeutic modality that it now is.

Burhenne devised a steerable catheter that has four cables embedded in its walls (A in Figure 6). The cables are attached to a base plate (B in Figure 6); the direction of the tip of the catheter can be changed by holding the base plate and exerting tension on the cables. With this procedure it is possible to alter the direction of the catheter tip and thereby guide it into the bile duct and in the direction of the stones sought. The steerable catheter most frequently used is a No. 13 F outside diameter; it is 25 cm long and is manufactured by Medi-Tech.‡

Several stone baskets are also necessary (C in Figure 6). Burhenne most frequently uses the

*Unread published material.

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Dormia* basket; it comes in only one size, but similar and adequate baskets are available from Cook† and Medi-Tech.‡

An extension tube (D in Figure 6) is attached to the end of the catheter and to a syringe filled with dilute iodinated contrast agent (E in Figure 6). Contrast material is injected several times during the procedure in order to see the stones and the position of the catheter tip.

The patient should have a T-tube (No. 14 F or larger) in place; this assures an adequate tract and easy passage of the steerable catheter into the duct after the T-tube has been removed. The T-tube should be brought out through a lateral, rather than medial, stab wound. This permits a shorter, straighter and therefore more easily negotiated tract. If the tract exits laterally, the radiologist's hands will not be in the way of the direct x-ray beam during manipulation. The T-tube should be left in place five weeks to guarantee the presence of a mature fibrous tract.

This procedure is done in the radiology department, using television monitored fluoroscopic control. The patients do not need to fast and no premedication is necessary. Most of Burhenne's patients were treated as outpatients. Prophylactic antibiotics are not used routinely; they are given only to those patients who have had a history of pancreatitis after surgery and to those patients with multiple intrahepatic stones, which may make manipulation difficult.

After a T-tube cholangiogram is obtained on the same day as the procedure and the presence of stones is verified, the T-tube is removed. By maneuvering the extending cables, the steerable catheter is manipulated into the biliary tree through the T-tube tract and positioned with its tip just distal to the stone. If several stones are present, the most distal stone is sought first.

The stone basket in its sheath is then passed through the lumen of the steerable catheter and the basket is opened distal to the stone. The open basket should never be advanced in the duct. The steerable catheter is pulled back. The opened basket should touch the walls of the duct. (The size of the basket used will depend on the size of the stone sought and the size of the duct.) The basket in then manipulated until it appears that the stone is engaged; the basket is not closed but is slowly withdrawn in the same position. Stones as large as 8 mm in diameter will pass readily through the tract. If stones are obviously larger, it may be necessary to fragment them either by closing the basket around them or by constructing a sling device. This sling is made by passing guide wires through an arterial catheter; the ends of the guide wires can then be manipulated by the radiologist.[56]

Stones or fragments of 4 mm or less in diameter may sometimes be aspirated through the steerable catheter by gentle suction or may be pushed into the duodenum by the catheter, but often they will spontaneously pass into the duodenum. Small stones may be difficult to retrieve by means of the basket because they are not easily seen on the fluoroscopic screen.

If the stones are in an unfavorable position, changing the position of the patient may occasionally displace the stone to a more satisfactory location. If a stone is impacted (for example, in the

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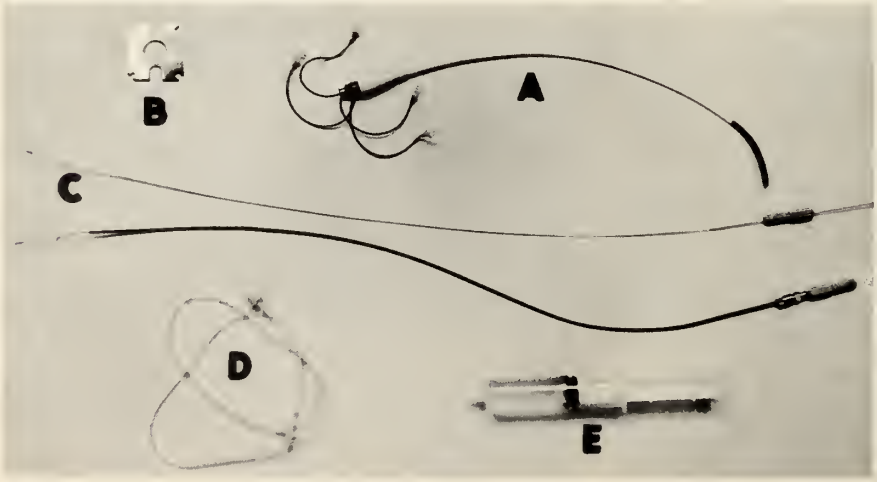

Figure 6.—Equipment necessary for nonoperative removal of biliary ductal stones. A = Burhenne steerable catheter—note four extending cables (Medi-Tech); B = base plate to which the catheter cables are attached; C = stone baskets (Cook)—small and large sizes, with the larger basket shown in its sheath; D = connecting tube; E = syringe containing iodinated contrast agent.

distal duct), gentle suction on the stone, passing a small catheter distal to the stone or placing the patient in the Trendelenburg position may alter the stone's position.

The patient should experience little discomfort during the procedure. Pain may be felt, however, if the ducts are distended rapidly with contrast agent or when a large stone is being extracted through the T-tube tract.

After extraction of as many visible stones as possible, a straight plastic tube is passed into the duct and a cholangiogram is obtained (Figure 7). If the study is unequivocally normal, the tube is removed and the patient is discharged. If there is any question about existence of a filling defect, whether it be stone, air bubble or blood clot, the straight tube is left in the bile duct and is taped in place, and the patient in instructed to return for a follow-up cholangiogram in one week. A tube is also left in place (if excessive manipulation has been done around the ampulla) to allow any possible ampullary edema to subside. If the study is normal on the follow-up cholangiogram, the tube is removed and the patient is discharged. If stones are still present, another attempt at extraction is made.

Multiple sessions have been necessary in about a third of Burhenne's patients.[57] In a patient with a small T-tube tract, the radiologist may dilate the tract during the first session and extract stones at another session. In the patient with multiple stones, although several stones may be removed, multiple filling defects may still be present. Air bubbles, blood clots and stones may all be present and may be difficult to differentiate. A tube is placed in the duct, and the patient returns after one week when confusing bubbles and clots will be gone and remaining stones can be retrieved more easily. For one of Burhenne's patients, four sessions were necessary to remove 24 stones from the biliary tree. Also, a stone located in an unfavorable position at the first attempt may move to a position where it can be more readily extracted when the patient returns.

The average length of the procedure at each session is about 45 minutes. In the average case, Burhenne estimates the amount of radiation to the skin in the area of manipulation to be approximately that of two barium enemas. The duration of fluoroscopic exposure will naturally shorten as the examiner becomes more experienced.

In Burhenne's series, the success rate has been 95 percent;[58] only 5 percent of the patients in whom this procedure was carried out had to return to surgery for removal of retained stones. Many of the failures were at the beginning of his series. Most of the more recent failures have been in patients in whom the T-tube tract was smaller than 14 F, or exited in a midline position giving a long and tortuous tract, and in patents in whom multiple intrahepatic stones were present distal to a strictured area.

Figure 7.—Incidence of biliary cutaneous fistula and retained stones in a 72-year-old man. **A**, Sinogram of left upper quadrant abdominal wall opening shows a fistula to the left hepatic duct. Multiple retained calculi in the intrahepatic ducts and common hepatic duct are present. A T-tube is in place. **B**, T-tube cholangiogram before Burhenne stone removal (T-tube had been in place 12 weeks). Multiple stones are now present in the common hepatic duct with no significant filling of the intrahepatic ducts. Left hepatic ductal-cutaneous fistula has healed. **C**, Cholangiogram done through a straight plastic tube, after removal of four large stones, shows no residual calculi and good filling of intrahepatic radicles.

The complication rate is 5 percent.[58] There have been no bile duct perforations and Polack and associates[59] have reported one fatality due to acute pancreatitis. Fever is the most frequent complication; sepsis has occurred in three patients. Patients with these complications were treated with antibiotics, and prompt remission was observed within 24 hours. Other rare complications have been sinus tract perforation, stone lost in a sinus tract, subhepatic bile collection and pancreatitis. One patient had to be returned to surgery after the stone basket had engaged a small intraductal neoplasm and the basket could not be extracted.

In summary, the Burhenne method of nonoperative extraction of retained biliary calculi should be the primary therapeutic procedure in patients with retained biliary calculi who have a T-tube in place. The success rate is an impressive 95 percent. There have been no fatalities, and the complication rate is 5 percent. This is an outpatient procedure and fasting or premedication is not necessary; equipment is easily available. If the prerequisites are heeded, a high rate of success seems assured.

DR. LONGMIRE: *Finally, Dr. Tompkins will discuss current efforts to decrease the incidence of retained stones by endoscopic examination of the ductal system after exploration and by improved techniques of operative cholangiography. Doctor Burhenne[52] noted that, even in retrospect, the operative cholangiograms of 80 percent of his patients with retained stones were of such poor quality that the stones could not be identified. Motion, poor positioning, overexposure and underexposure, as well as insufficient contrast filling of the major hepatic radicals, were the chief factors responsible for the failure of the x-ray studies. Dr. Tompkins will outline the important principles of operative cholangiography.*

RONALD K. TOMPKINS, MD:* Development of better methods for preventing retained common duct stones is to be preferred to improvement of operative techniques for removing them. There have been dramatic improvements in our ability to prevent overlooked common duct stones. These involve primarily two methodologies: routine cystic duct cholangiography with every cholecystectomy and operative choledochoscopy with completion T-tube cholangiography when the common duct has been opened and surgically explored.

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Prevention of Common Duct Stones

Cystic Duct Cholangiography

There is now sufficient evidence from many clinical series to support the recommendation that cystic duct cholangiography be made a routine part of every cholecystectomy.[60-63] Not only will unsuspected common duct stones be found by this method in 4 percent to 7 percent of patients, but also, in the patient with known common duct stones, cystic duct cholangiography done before opening the common duct may provide valuable information about the number and position of the stones.

As described previously, the technique of cholangiography is relatively simple.[63] Technical innovations, such as fluoroscopy in the operating room, are expensive but hold promise of reducing the already small numbers of false-positive and false-negative studies. Properly done, routine cystic duct cholangiography should reduce by 50 percent the incidence of retained common duct stones, that is, the proportion of those stones that occur because the duct has not been explored.

Operative Choledochoscopy and Completion T-Tube Cholangiogram

Recent improvements in instrumentation for visualization of the interior of the bilary system have dramatically advanced the ability of the surgeon to assure that the duct is free of stones before closing the common duct.[64] A recent multiinstitutional cooperative study of the results of choledochoscopy and T-tube cholangiography in patients in whom common duct exploration was done shows that the incidence of unsuspected retained stones was only 1.9 percent as compared with reported incidences of 9 percent to 14 percent in other large series.[65] Further experience with the operative choledochoscope (to supplement preexploration cystic duct and postexploration T-tube cholangiographies) will probably greatly reduce the occurrence of retained common duct stones in patients who require open exploration of the common duct.

Other Aspects of Prevention

Earlier operation for gallstone disease is also an effective way of preventing common duct stones. Wenckert and Robertson[66] pointed out

that, in patients who underwent surgical operation within one year of the diagnosis of gallbladder stones, the incidence of common duct stones was 16 percent. In a similar group of patients who delayed operations as long as 11 years after the diagnosis, common duct stones were found in 27 percent. Similar statistics have been found by us in a review of more than 2,800 biliary tract operations (R. K. Tompkins, MD, unpublished data, 1969). The old adage that the longer one has gallstones the more likely the complications from them is borne out by these data. Earlier operation on patients with cholelithiasis should help prevent the possible grave complications of common duct stones.

Operative Removal of Retained Common Duct Stones

Failing in his attempts to prevent and, subsequently, to remove nonsurgically the patient's retained common duct calculus, the surgeon is faced with the decision as to which operative approach to take. There are three operative procedures to be considered: choledochotomy alone, sphincteroplasty and a duct-enteric anastomosis.

Choledochotomy Alone

This approach is probably best suited to the patient who has a retained common duct stone and in whom the common duct has *never* been explored, that is, the patient who did not have cystic duct cholangiography at the time of cholecystectomy and who did have a common duct stone. For all other patients, most surgeons will probably elect sphincteroplasty or a duct-enteric anastomosis.

Sphincteroplasty

This procedure (as a form of duct-enteric anastomosis) is favored by many surgeons because of their training and experience.[67] It is difficult to define a rigid set of indications and contraindications for sphincteroplasty. One of the most frequent indications is a stone impacted in the ampullary region. The prominent contraindications include a duct emptying into a duodenal diverticulum or the presence of pancreatitis. A patient who has had a previous sphincteroplasty and then has recurrent stones would not be a suitable candidate for a repeat operation in this area. Such patients and those who have intrahepatic duct stones will probably best be served by a formal duct-enteric anastomosis.

Duct-Enteric Anastomosis

In the United States most of the patients who have retained common duct stones after a previous choledochotomy (or choledochotomies) are treated by duct-enteric anastomoses. Whether this is a choledochoduodenostomy or Roux-en-Y choledochojejunostomy depends primarily on the surgeon's prejudices and experience with one or the other procedure. In a recent retrospective review, McArthur and Longmire[68] found the operative mortality, fistula rate and stricture rate to be higher for choledochoduodenostomy than for choledochojejunostomy. The latter procedure, however, was associated with a higher prevalence of postoperative peptic ulcer disease. The preference at UCLA has been for the duct-jejunal anastomosis done in Roux-en-Y fashion, although surgeons in other parts of the country prefer the choledochoduodenostomy.[69]

In summary, the best treatment for retained common duct stones is their prevention at the time of the original surgical operation. Advances in technology related to operative x-ray studies and endoscopy have helped in assuring that all stones have been removed from the biliary system. If preventive measures fail, all reasonable nonoperative methods of stone removal should be attempted before operative therapy is begun, unless the clinical condition of the patient demands an early reoperation.[32,70]

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Techniques in Treatment of Retained Gallstones

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A PANEL DISCUSSION of the treatment of retained gallstones precedes this editorial comment. Most investigators feel that approximately 5 percent of all patients in whom cholecystectomy is done will have retained gallstones in the extrahepatic bile ducts following the operation. If we assume that 600,000 cholecystectomies are carried out each year in the United States, there would be about 30,000 patients with retained stones in this country, compared with the 3,000 or 4,000 mentioned by Dr. Longmire. Therefore, any discussion of the nine new modes of evaluation and treatment for common bile duct stones is timely. The nine new modalities are (1) ultrasound, (2) computerized axial tomography, (3) percutaneous transhepatic cholangiography with a small needle, (4) endoscopic retrograde cholangiopancreatography, (5) manometric cholangiography, (6) operative choledochoscopy, (7) dissolution of common bile duct stones with mono-octanoic acid, (8) removal of stones with a directable stone basket and (9) endoscopic papillotomy. It is appropriate to discuss the place of each modality in the preoperative, operative, early postoperative and late postoperative periods in relation to the diagnosis of gallbladder and common bile duct stones. Any of these modalities, with the exception of operative manometric cholangiography, choledochoscopy, and dissolution of intraductal stones by irrigating with a solution, can be used in the preoperative period and in the late postoperative period after all tubes are removed.

Diagnostic ultrasound and computerized axial tomography (CAT) of the upper abdomen have offered the first good, noninvasive techniques of evaluating the gallbladder and the intrahepatic and extrahepatic bile ducts for enlargement, distortions or contained gallstones. At present, ultrasound seems about as efficacious as CAT in thin patients without ascites, and it costs about a fourth as much,[1] without involving radiation. This technique is subject to considerable variation in quality from institution to institution. High-quality results require expert technicians to assure good imaging by this technique, as well as a well-tuned instrument and physicians capable of reading the output. Each cut made by a CAT scan must be done within five to ten seconds in order to eliminate the blurring resulting from respiratory motion in a long exposure. This instrument is effective in cases in which large amounts of intraabdominal gas are present, as well as in obese patients—as compared with ultrasound in which the sound is reflected by gas-containing structures and adipose tissue. Most centers now prefer diagnostic ultrasound because of its near-equivalence in efficacy, because it is cheaper, and because it does not involve radiation. We believe that this technique should be the first one used in the preoperative or late postoperative evaluation of a patient with presumed obstructive jaundice.[2]

Percutaneous transhepatic cholangiography (PTC), a procedure that has been used in a few centers for almost 40 years, has recently been repopularized as a method for distinguishing among obstructive jaundice, surgical jaundice and jaundice due to inflammatory or chronic liver disease in patients in the preoperative or late postoperative period. We believe that the approach of using a small, light, flexible skinny needle for such patients is as safe as Dr. Goldstein has stated in those patients shown by diagnostic ultrasound or CAT scans to have bile ducts of normal diameter. It seems to us that, in this procedure as well as in endoscopic retrograde cholangiopancreatography (ERCP), the procedure should be done in patients with hepatic bile ducts dilated to more than 1 cm in diameter only when percutaneous[3,22,23] or operative drainage of the biliary system[4] is planned to

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be carried out immediately or shortly afterward. We have found that the complications of cholangitis or bile peritonitis following percutaneous cholangiography are much more common in the presence of dilated partially obstructed ducts.[5,6] We are not sure whether percutaneous cholangiograms are preferable to minilap or ERCP as the primary invasive procedure for the evaluation of the obstructed duct. There is some likelihood of introducing infected material above a point of partial or total obstruction in all three approaches. PTC will show where stones are located as well as where deformities occur within the ductal system. ERCP should be used when PTC is not successful or is contraindicated because of problems of bleeding. This procedure is especially effective in differentiating among different types of lesions of the lower bile ducts and may be used in instances where PTC has failed or the ducts are extremely small. ERCP can also add information regarding the status of the pancreas and ampulla of Vater which would not be possible with PTC.

Manometric cholangiography and operative choledochoscopy seem to us to be the principal new contributions to the operative evaluation and treatment of patients with common bile duct stones. We do not feel that endoscopic papillotomy now has a place as a primary procedure. We will discuss this modality in more detail later. Operative cholangiography has been supplemented by manometry and image intensification in Europe and South America for about 30 years and is becoming increasingly popular in the United States. Manometry is valuable because it can show that stones or strictures in the distal bile duct cause increased intraductal pressure and decreased flow through the sphincter of Oddi. Our prospective studies on manometric cholangiography have shown that about 7 percent more common bile duct stones could be found if routine manometry supplemented operative cholangiography.[7] Most of these stones could not be seen even after a retrospective view of the operative cholangiograms. We wonder whether or not the addition of the very expensive image-intensification apparatus recommended by Berci and Tompkins will be cost effective in finding small stones.[8]

Operative choledochoscopy can be used only in patients whose ducts are more than 5 mm in diameter, in which situations the rigid Storz choledochoscope is used, and where the ducts are 18 to 20 mm in diameter if the fiberoptic instrument is used.[9,10] We have found the Storz instrument useful in finding stones that are difficult to locate by blind probing and exploration since it literally lends an eye to the exploration of the common bile duct. This approach has been shown to be especially effective in assisting in the removal of multiple stones in very large ducts. The usual grasping forceps and ureteral baskets or forceps can be passed through a special side channel to retrieve stones. We have found that this instrument is as effective as the flexible fiberoptic instrument advocated by Yamakawa.[10] It costs about a sixth as much as the flexible instrument and is much easier for the uninitiated to maneuver. We now feel that the best operative approach to evaluating the common bile duct is through the use of manometric operative cholangiograms followed by endoscopy and a T-tube cholangiogram after the removal of common bile duct stones.

The third phase in the detection and removal of residual common bile duct stones is in the postoperative period. Such stones can be detected by routine postoperative T-tube cholangiograms in those patients in whom the common bile duct has been explored. Elevated intraductal pressures and decreased flow are also indicators of residual obstruction, as they are during the operative period. Attempts to dissolve common bile duct stones have been largely unsuccessful in the past. Bile salt solutions in concentrations of 100 to 200 mM have been effective in dissolving about two thirds of residual cholesterol stones in the common bile duct.[11] This type of treatment requires admission to hospital for six to ten days, and has often been accompanied by such severe diarrhea that oral administration of cholestryramine was necessary. Furthermore, these solutions are reported to cause the appearance of a ragged contour in the hepatic duct after several days of irrigation.[12] Heparin has been reported by Gardner[13] to cause the disappearance of common bile duct stones, allegedly due to a change in electrical charge in such stones. Most other investigators feel that the disappearance of such stones under these circumstances is probably due to physical lavage rather than to a specific effect of the heparin solution, because heparin solutions do not dissolve cholesterol. Recently mono-octanoin has been used in a small series of patients by Thistle and Hofmann[12] and ourselves.[7] This material is thought to be more effective in the dissolution of common bile duct stones than is cholic acid, without the toxic side effects. It is currently under investigation.

At about the same time these dissolving solutions were introduced, instruments were developed by Mondet,[14] Mazzariello[15] and Burhenne[16] for the nonoperative instrumental extraction of retained stones from the bile duct during the early postoperative period. All three authors report successes in about 95 percent of attempts. This particular technique and that of irrigation of the bile duct with dissolving solutions should be delayed for six to eight weeks following the surgical operation in order to allow for formation of a solid scar along the T-tube tract. The stones can then be withdrawn using a Dormia basket or a stone forceps, or they can be crushed by a special instrument and then withdrawn by one or another of several directable instruments that can be placed down through the tract into the common bile duct. This technique has been so successful that there is some question as to whether irrigation of the common bile duct with dissolving solutions will be necessary in many instances in the future. Yamakawa has another approach to removing such stones: Putting a flexible endoscope down the T-tube tract allows him to extract residual stones under direct vision.[10] This device has disadvantages. It requires a fairly large turning radius to function properly, necessitating the placement of a T-tube that has a vertical limb 18 F in diameter or larger. The instrument is much more expensive than the others, with the additional disadvantage that glass fibers break with prolonged usage and become yellow after exposure to x-rays. If one or the other of these misfortunes occurs, the instrument becomes unusable.

Finally, endoscopic papillotomy has enjoyed enormous popularity in Germany, France and Belgium,[17-19] where a recent analysis indicates that 2,304 papillotomies have been done, with a reported 95 percent success rate in causing passage of stones.[20] This approach appears justified as an emergency procedure in patients who are seriously ill with cholangitis or septicemia, in the elderly and debilitated and in those who refuse gallbladder removal. It can also be used to assist in the removal of stones from the common bile ducts of patients in whom postoperative jaundice develops that is obstructive in nature and in whom the common bile duct was not explored and no T-tube is in place. At present this technique is considered experimental in the United States.

The incidence of retained or recurrent common bile duct stones following cholecystectomy may be even greater than the 30,000 cases per year suggested at the beginning of this comment, since stones are frequently asymptomatic and very few prospective series have been carried out on this subject. A recent Swedish autopsy series of patients who had previously undergone cholecystectomy indicated that 11 percent had retained or recurrent duct stones.[21] It is astonishing that the incidence of recurrence is not higher. The techniques described above may assist us in reducing the number of retained stones with their consequent obstructive complications, need for reoperations and suffering and pain.

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Refer to: Layzer R: Myasthenia gravis—Medical Staff Conference, University of California, San Francisco. West J Med 130:438-443, May 1979

Myasthenia Gravis

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. SMITH:* *Recently, a patient in the intensive care unit with myasthenia gravis was treated with plasma exchange, the first time this treatment had been used for myasthenia in this hospital. Now seems to be an opportune time to have Dr. Robert Layzer review myasthenia gravis and describe some recent advances in our understanding of the pathogenesis of this neurological condition.*

DR. LAYZER:† Treatment of myasthenia has made steady progress through the years, but until recently knowledge about pathogenesis and treatment remained more or less separate, although they now seem to be converging rapidly.

I thought that the best way to review this subject would be to go back to 1960, which was a turning point for the modern understanding of myasthenia gravis, and to trace historically the development of ideas since then. First, it was known in 1960 that myasthenia was a disorder of neuromuscular transmission, partly relieved by anticholinesterase drugs, but it was not certain whether the defect represented a poor response to nerve stimulation—that is, an abnormality on the postsynaptic side of the neuromuscular junction—or a presynaptic defect in the release of acetylcholine from the nerve terminal. Second, it was known that about 10 percent of patients with myasthenia gravis had a thymoma, and that those who did not have a thymoma usually had hyperplasia of the thymic lymphoid tissue.[1] Third, it was generally agreed (though the statistical evidence was somewhat weak) that removing the thymus gland in patients who did not have a thymoma was an effective form of treatment for myasthenia gravis.

To expand a little, it should be recalled that before 1960 the postoperative course of myasthenic patients was often stormy because of the primitive state of facilities for assisting ventilation. After the introduction of positive pressure ventilation in the late 1950's, thymectomy assumed increasing importance in the management of myasthenia, especially for patients who had more than minor symptoms. Table 1 lists the results of thymectomy in a recent study done at the Mayo Clinic.[2] Like other retrospective surveys of thymectomy in myasthenia gravis, it is somewhat lacking. However, the authors used a computer to match 80 surgically treated patients with 80 patients who were not operated on, so that the two groups were comparable in every important respect, including severity and duration of disease. The average duration of follow-up was approximately 20 years. As one can see, the number of patients in remission was four to five times higher in the group of surgically treated patients, the number of improved patients was double, and the number dead was less than half.

*Lloyd H. Smith, Jr., MD, Professor and Chairman, Department of Medicine

†Robert Layzer, MD, Professor of Neurology

TABLE 1.—*Results of thymectomy in 80 patients, compared with 80 matched patients who were not surgically treated. All patients were older than 16 years and were treated at the Mayo Clinic before 1965. The average follow-up was between 20 and 23 years.**

Status	*Surgical Group (80)*	*Medical Group (80)*
Complete remission	27	6
Improved	26	13
Unchanged	3	7
Worse	1	5
Dead	21	47
Myasthenia gravis	11	34
Other causes	10	13
Lost to follow-up	2	2

*Reproduced from Buckingham et al with permission from Ann Surg.[2]

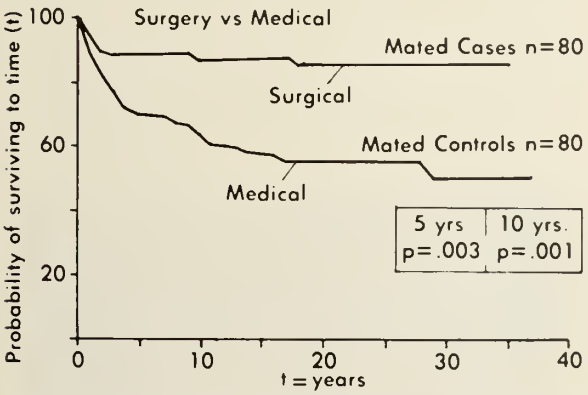

Figure 1.—Survival curve showing the effect of thymectomy in myasthenia gravis. (Reproduced from Buckingham JM et al, with permission from Ann Surg.[2])

Figure 1 shows these data in a survival curve; the increased death rate in cases without operations appeared to continue for about 15 years following the beginning of the study. Other studies, from many other institutions in several countries, have provided similar results. Now thymectomy is generally accepted as the treatment of choice in disabling myasthenia, and most authorities recommend that it be carried out early in the course of the disease, although there is little evidence to support the last point.[3]

Another important fact known in 1960 was that babies born to mothers with myasthenia gravis occasionally exhibited transient symptoms of myasthenia in the immediate postnatal period.[4] The weakness tended to be mild but sometimes required treatment with anticholinesterase drugs, and always disappeared in a few weeks. This transient neonatal myasthenia made many suspect that a circulating substance, capable of being transferred across the placenta, was present in the plasma of patients with myasthenia gravis. Through the years there were several attempts to show neuromuscular blocking activity in myasthenic serum by testing its effect on neuromuscular transmission in animals, either *in vitro* or *in vivo*. During one such study in the late 1950's, a medical student, Arthur Strauss, working at Columbia University with William Nastuk, discovered a cytopathic effect of myasthenic serum on muscle in frogs. This finding led to the discovery that circulating antibodies reacting with skeletal muscle were present in 30 percent of myasthenic patients, in 95 percent of patients with both myasthenia and thymoma, and in 24 percent of patients with thymoma who did not have myasthenia.[5,6] The antibodies reacted with the cross striations of muscle, not with the neuromuscular junction, which could not easily explain the physiological disorder. They also reacted with the epithelial cells of the thymus, a type of cell that was later discovered to be a primitive muscle cell, mysteriously present in the thymus gland of humans and lower animals. In 1960 Nastuk and Strauss published their hypothesis, based on the findings of these immunological studies, that myasthenia gravis was an autoimmune disease.[5]

Coincidentally, in the same year, J. A. Simpson, a Scottish neurologist, published in the *Scottish Medical Journal* a lecture in which he also proposed that myasthenia gravis was an autoimmune disease.[7] Arguing from clinical observations, he supposed that a circulating antibody was present which reacted with the acetylcholine receptor on the postsynaptic surface of the neuromuscular junction. This clairvoyant prediction was prompted by an apparent association that Simpson had detected between myasthenia gravis and certain immunological disorders, such as rheumatoid arthritis and pernicious anemia.

After the autoimmune theory was promulgated in 1960, some years went by before new supporting evidence was introduced. The next major advances, in fact, did not relate directly to the immunological question but to questions involving physiology and pathology. From 1950 to 1960 the details of neuromuscular transmission were clarified. A diagram of the neuromuscular junction is shown in Figure 2. The postsynaptic region of the muscle is arranged in deep folds forming troughs, at the mouths of which lie the acetycholine receptors. The nerve terminal contains many synaptic vesicles, each containing

several thousand molecules of acetylcholine. When a nerve impulse invades the nerve terminal, the contents of 50 to 100 synaptic vesicles are released simultaneously, producing a large depolarization of the postsynaptic membrane. At rest, however, individual packets of acetylcholine are also released spontaneously, at the rate of about one per second. These spontaneously released packets of acetylcholine produce small depolarizations of 0.5 to 1.0 mV in the postsynaptic membrane potential as recorded by a microelectrode in that region. The term *miniature end-plate potentials* is applied to such depolarizations. In 1964, Elmquist and his colleagues,[8] studying intercostal muscle biopsy specimens, showed that in myasthenia gravis the amplitude of the miniature end-plate potentials averaged a fifth of the normal amplitude (Figure 3). This striking abnormality could have resulted from a poor response of the postsynaptic membrane to acetylcholine or from a reduced release of acetylcholine from the nerve terminal; it was not immediately apparent which explanation was correct.

Seven years later, in 1971, Engel and Santa[9] helped to answer this question with their histometric studies of the electron-microscopic appearance of the neuromuscular junction, Figure 4. In many myasthenic end-plates the postsynaptic structure was quite abnormal, with considerable loss of membrane surface area and great simplification of the synaptic folds. In places, debris from the disintegration of the postsynaptic membrane was seen lying within the synaptic clefts.

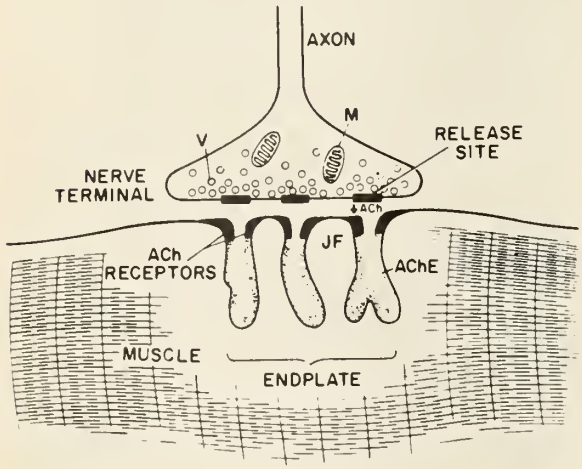

Figure 2.—Diagram of neuromuscular junction. Vesicles (V) release their acetylcholine (ACh) contents at specialized release sites. After crossing the narrow synaptic space **(path indicated by arrow)** ACh reaches the ACh receptors, which are situated most densely at the peaks of the junctional folds (JF). Acetylcholinesterase (AChE) in the clefts rapidly hydrolyzes the ACh. M denotes mitochondria. (Reproduced from Drachman DB, with permission from N Engl J Med.[13])

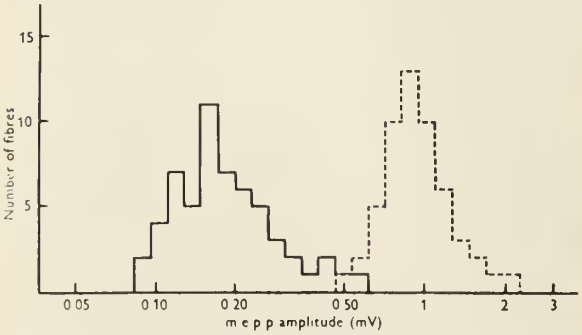

Figure 3.—Distribution of mean miniature end-plate potential (m.e.p.p.) amplitudes recorded from 57 myesthenic **(solid line)** and 54 normal **(broken line)** intercostal muscle fibers. Note logarithmic scale of abscissa. (Reproduced from Elmqvist D et al, with permission from J Physiol.[8])

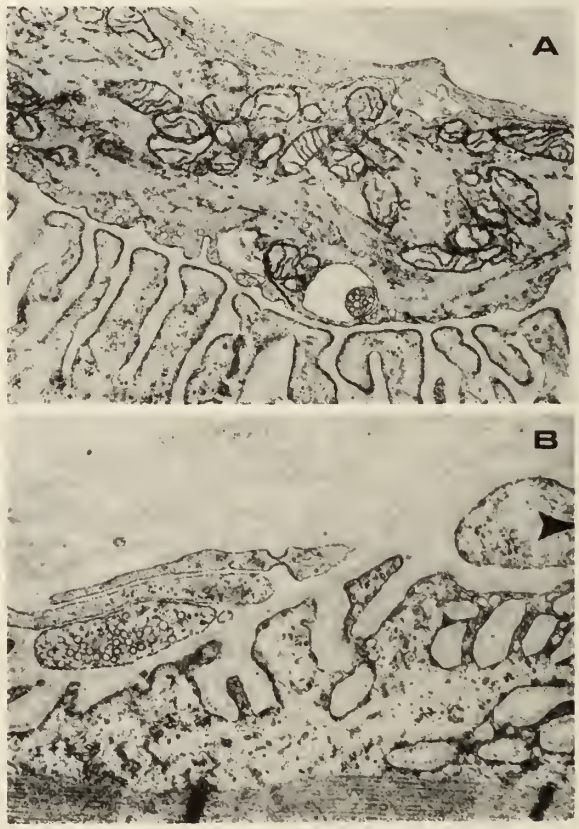

Figure 4.—Ultrastructure of neuromuscular junction in myasthenia gravis. **A**, a normal end-plate with numerous deep synaptic clefts formed by folding of the postsynaptic membrane. **B**, a myasthenic end-plate with shallow, sparse synaptic clefts. (Reproduced from Engel AG et al, with permission from Ann NY Acad Sci.[9])

The overall impression was of a degenerative process principally affecting the postsynaptic portion of the end-plate.

Meanwhile, a new phase in treatment was under way, perhaps inspired by the autoimmune hypothesis. In the late 1960's it was found that a short course of adrenocorticotrophic hormone (ACTH) in high doses caused a transient increase in myasthenic weakness, after which, for a period lasting a few weeks or months, patients became stronger than they were before treatment.[10] In 1972 the use of continuous high-dose prednisone treatment was introduced,[11] quickly replacing ACTH therapy. In most patients there was dramatic improvement, although during the early phase of treatment regression was often seen. It has been suggested that prednisone and other corticosteroids have a direct neuromuscular-blocking effect, but this has not been well established. After the condition of a patient improves, the harmful effect of prednisone is no longer prominent.

Long-term treatment with prednisone is now a major factor in the management of severe myasthenia gravis.[12] My view is that corticosteroid treatment should be reserved for patients who have disabling or life-threatening symptoms, usually after thymectomy has been done. It is unfortunate that in many patients there is no improvement for several years after thymectomy; therefore, therapy with prednisone often provides effective relief in those patients with severe myasthenia gravis in whom thymectomy has not been effective. In most patients, I initiate treatment with 40 to 60 mg of prednisone per day in divided doses, changing to an alternate-day schedule after improvement occurs, usually within three months. Slow tapering of the dosage is usually possible. Many patients regain normal muscular function during treatment, but there is no evidence that administration of prednisone shortens the duration of the disease. In other words, there is no reason to think that prednisone has a curative rather than a suppressive effect.

In 1973 myasthenia research advanced in a new direction, largely because of a snake venom called bungarotoxin.[13] This paralyzing protein binds specifically and irreversibly to the nicotinic acetylcholine receptor of many different organisms, from humans to electric eels. Recognizing this fact, investigators in several laboratories began to use bungarotoxin and related toxins for two purposes: (1) using affinity chromatography to purify the acetylcholine receptor, which is plentiful in tissues of electric eels and electric fish and (2) using bungarotoxin labeled with radioactive iodine (^{131}I) to study the number and turnover of acetylcholine receptors in muscle under a variety of experimental conditions. Fambrough and associates[14] estimated the number of acetylcholine receptors in myasthenic muscle by counting the radioactivity of bungarotoxin ^{131}I bound after incubation with an intercostal muscle biopsy specimen. In myasthenic end-plates, bound bungarotoxin radioactivity (measured directly or by autoradiography) was reduced to between 10 percent and 20 percent of normal. This was the first direct evidence that the defect of neuromuscular transmission in myasthenia gravis is postsynaptic, settling a controversy that had continued for several decades.

Meanwhile, at the Salk Institute, Patrick and Lindstrom[15] were purifying the acetylcholine receptor from electric eels. Intending to prepare antibodies against the purified receptor, they injected the receptor, emulsified in Freund's adjuvant, into rabbits. Within three weeks after the second injection several rabbits became paralyzed. The paralysis was reversed through the administration of anticholinesterase drugs, and repetitive nerve stimulation showed a decrementing response similar to that seen in myasthenia gravis. Patrick and Lindstrom realized that they had inadvertently created an experimental autoimmune model of myasthenia gravis. The new disease model was quickly adopted by other investigators, and the pathogenesis of the experimental disease was soon clarified.[16]

Following immunization with the acetylcholine receptor, there was a lymphocytic invasion of the end-plate region, leading to structural damage to the postsynaptic membrane concentrated at the mouths of the folds where the acetylcholine receptor is located. Next, antibody appeared in the blood, and a phase of continuing minor damage ensued, associated with persistent levels of antibody in the blood. It is interesting that the antibodies reacted primarily with the foreign species of acetylocholine receptor used for immunization, but later antibodies were more reactive with the animal's own acetylcholine receptors.

The next step was to search for antibodies acting against acetylcholine receptor in the serum of patients with myasthenia gravis. In the past all such attempts had been unsuccessful, but in

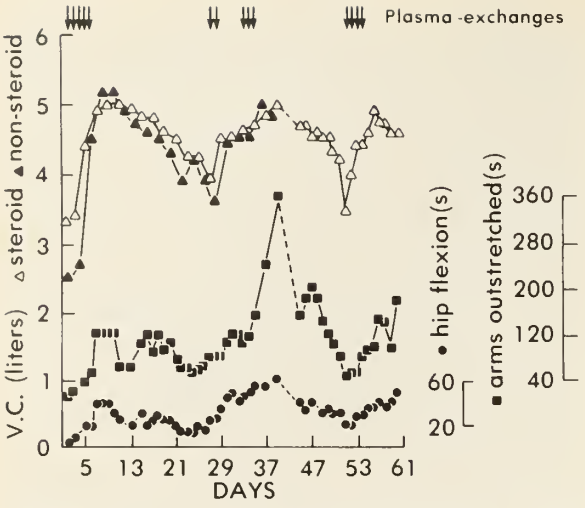

Figure 5.—Effect of plasma exchange therapy on muscle strength in a myasthenic patient receiving alternate-day prednisone treatment. Vital capacity (V.C.) and limb strength (recorded as number of seconds held up against gravity) improved transiently following each course of plasma exchanges. Three sets of plasma exchange (all of 2 litres) are marked, the second set being divided into two parts. Administration of pyridostigmine bromide was stopped on day 9; reduction in steroid dosage started on day 15. The dotted line indicates a time when measurements were not possible; after this time steroids were given every day. (Reproduced from Pinching AJ, with permission from Lancet.[21])

1974 and subsequently, new techniques, based on the use of bungarotoxin ^{131}I, enabled groups led by Appel,[17] Lindstrom[18] and others to detect antibodies to acetylcholine receptor in 80 percent to 90 percent of patients with myasthenia gravis. There is only a very rough correlation between the titer of these antibodies and the severity of the disease, but patients with purely ocular myasthenia lack antibody more often than those with generalized myasthenia gravis. Following thymectomy or steroid therapy, levels of antibody tend to fall as the patient improves.

It was tempting to assume that these antibodies played a role in causing myasthenia gravis in humans. However, might they not simply be an epiphenomenon—the result of damage to the motor end-plate rather than the cause? To answer this question, Drachman and colleagues,[19] in 1975, injected large amounts of a globulin fraction of myasthenic serum into mice. They found that the amplitude of miniature end-plate potentials was reduced more than 50 percent, and many of the mice appeared weak—an effect not found with normal human serum. Meanwhile, in 1973 Bergstrom and associates[20] reported that continuous drainage of lymph from the thoracic duct of myasthenic patients resulted in temporary improvement, which could be reversed by infusion of the cell-free lymph or of an immunoglobulin fraction of the lymph. This observation led to the most dramatic recent development in the treatment of myasthenia. In 1976 Pinching and co-workers[21] reported temporary but striking improvement of weakness in three myasthenic patients treated with plasma exchange (Figure 5). Later the authors documented a fall in antibody titers during the clinical improvement, and a rise in titers as symptoms returned.[22] The beneficial effect could be prolonged in many cases by immunosuppressive therapy at the time of plasma exchange. Similar results have been reported by Dau and associates in San Francisco.[23] Plasma exchange (plasmapheresis) is now being used rather widely, but primarily as a temporary treatment for seriously ill patients while awaiting the benefits of the slowly acting immunosuppressive drugs.

These results leave little doubt that serum antibodies play a continuing pathogenic role in most patients with myasthenia. How do the antibodies exert their harmful effects? Although the structural damage at the motor end-plate, which is a pathological feature of myasthenia, could be antibody mediated, it seems unlikely that this damage could be repaired quickly enough to account for the early clinical response to plasma exchange. The antibody could have a simple receptor-blocking action, like curare, but Engel and co-workers[24] cast some doubt on this explanation. In 1977 they showed that immune complexes (IgG and the C3 component of complement) are deposited on the postsynaptic membrane of myasthenic motor end-plates. The length of postsynaptic membrane containing either IgG or C3 was directly proportional to the size of miniature end-plate potentials, as determined by electrophysiological measurements (Figure 6). Therefore, the more antibody found at the end-plate, the better was neuromuscular transmission. Presumably the antibodies, like bungarotoxin ^{131}I in earlier studies, provided an index of the number of available acetylcholine receptors without blocking transmission. Finally, it has been shown that myasthenic immunoglobulin accelerates the degradation of acetylcholine receptors,[25] and this process has a time course that could account for the rapid clinical response to the removal of antibodies.

We have seen how recent developments have led to a more or less rational approach to the

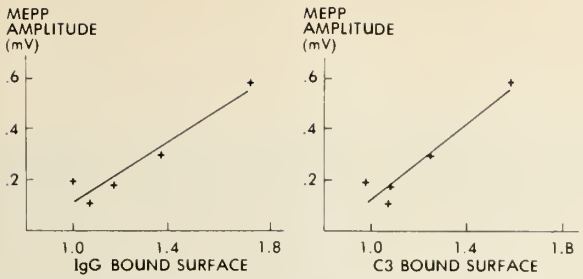

Figure 6.—Relationship between mean miniature end-plate potential (MEPP) amplitude and amount of IgG and C3 bound to postsynaptic membrane. Data are from intercostal muscle biopsies of five myasthenic patients. MEPP amplitude is directly proportional to the surface area occupied by immune complexes, suggest-that these complexes do not directly inhibit neuromuscular transmission. (Reproduced from Engel AG, with permission from Proc Mayo Clinic.[24])

treatment of myasthenia gravis as an immunological disorder. I think two major questions about pathogenesis remain for future research: What is the role of the thymus gland and what initiates the autoimmune reaction? A more specific way of reversing the immunological attack on the motor end-plate without interfering with normal defense mechanisms is needed for treatment of myasthenia. Judging from the rate of recent progress, we may not have to wait long for solutions to these problems.

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Important Advances in Clinical Medicine

Epitomes of Progress — Radiology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in radiology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in radiology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Radiology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Epidural Venography for Lumbar Disk Disease

THE EPIDURAL VENOUS PLEXUS was first visualized in 1954 when inadvertent catheter wedging occurred during cardiac catheterization. Since then, attempts at visualizing these veins have included lumbar spinous process intraosseous contrast injections and lower extremity venous injections. Because of inconsistent results and pain, these procedures did not gain popularity.

Gargano introduced the technique of selective ascending lumbar vein catheterization in 1974. This proved much more reliable and nearly painless. This procedure can generally be accomplished without admitting patients to hospital. Percutaneous puncture and catheterization of one or both femoral veins is carried out. One catheter tip usually is placed in an ascending lumbar vein (part of the external vertebral plexus) and an optional second catheter may be placed in the presacral plexus or opposite ascending lumbar vein. Iodinated water soluble contrast is injected with serial filming during abdominal compression and forced expiration. The patient may be released from the department within one to two hours.

The findings of extradural compression of the internal vertebral venous plexus include varying combinations of the following: (1) bilateral or unilateral occlusion of the veins at a disk level, (2) asymmetric focal distortion of the usually regular venous pattern, (3) occlusion or distortion

of a radicular vein, (4) focally abnormal flow dynamics.

A frankly herniated disk which is readily seen at myelography is nearly always easily shown by venography. Lateral disk protrusions may not deform the dura or arachnoid root sleeve and, therefore, may be missed at myelography. Theoretically (and actually, in most cases) these lesions will deform the epidural veins. Previous surgical operation at a given level, however, generally obliterates portions of the venous plexus and radicular veins making interpretation of venography at that level virtually impossible.

In one study with 55 patients, 28 disk levels were explored. Disk herniation was correctly indicated at 24 levels, for an accuracy of 86 percent. There were no false positives. Myelography was correct at 23 levels. The combined accuracy of both studies was 89 percent (25 levels). Venography and myelography were concluded to be equally accurate and complementary.

Lumbar epidural venography is a safe procedure for showing the extradural compressive effects of herniated lumbar intervertebral disks. Its best use in the current clinical setting probably lies in showing the presence and site of a lesion in a patient in whom there are positive clinical and electromyographic findings but negative or equivocal findings on a myelogram.

Because of the low morbidity and outpatient nature of the examination, some might find this study an attractive initial screening procedure for a patient with strong focal symptomatology. Myelography should be considered a complementary examination.

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O'Dell CW Jr, Coel MN, Ignelzi RJ: Ascending lumbar venography in lumbar-disc disease. J Bone Joint Surg 59:159-163, Mar 1977

Computed Tomographic Scanning of the Larynx

THE TASK OF RADIOLOGY in evaluating laryngeal masses is to determine the extent of disease. If the mass turns out to be malignant such information helps to determine the feasibility of conservation surgical therapy or the planning of precision radiation therapy. Some of the critical areas of interest in making this decision include the subglottic region (especially the cricoid cartilage), the anterior commissure, the cricoarytenoid joint and the interarytenoid areas. The cricoid cartilage is vital since it is the supporting structure of the entire larynx. The cross-sectional image of computed tomographic (CT) scanning provides excellent visualization of all of these critical regions. Moreover, computed tomography shows the deep tissue planes surrounding the true cords, false cords and subglottic space (paralaryngeal space). Kirchner's work shows that tumors of the larynx extend along the deep tissue planes and will spread throughout the paralaryngeal space to gain access to the preepiglottic space or invade cartilage, or both. These spreads can only be implied from positive contrast laryngography or pleuridirectional tomograms by a lack of mobility of the cords or entire larynx. In our hands xeroradiography has shown less than half of the instances of cartilage invasion by comparison to CT scanning.

Clinically, indirect and direct laryngoscopy show most of the mucosal surfaces (except those of the subglottic space and most inferior tips of the pyriform sinuses) and provide a good evaluation of glottic function, but the deep planes are again not directly visualized. Laryngography, for the most part, duplicates the information concerning function and mucosal surfaces gained by these clinical examinations.

CT scanning has essentially no morbidity (save the radiation exposure) and complements the direct laryngoscopic examination nicely. The examination is best made during quiet breathing, starting at the level of the anterior ring of the cricoid cartilage and proceeding cephalad at 5 mm intervals to the level of the hyoid bone.

Experience to date also indicates that CT provides a sensitive and complete evaluation of the traumatized laryngotracheal complex. This includes a detailed evaluation of the thyroid cartilages, cricoid ring and arytenoids. The extent of soft tissue injury and the related encroachment on the airway are readily apparent. Its lack of morbidity provides an additional benefit in acutely injured patients.

In summary, CT scanning of the larynx provides a safe, extremely informative examination of the larynx in cases of mass lesions and laryngeal trauma. At our institution, CT scanning is not just another test to be added to the workup but is replacing xeroradiography, tomography and

positive contrast laryngography in the evaluation of patients with cancer of the larynx.

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Reducing Dosages in Film Mammography

CONTROVERSY over the possible hazards of diagnostic x-ray examinations has been more evident in mammography than in any other area of diagnostic radiology. Despite the lack of direct evidence that induction of carcinoma may result from mammography, the possibility of risk has become generally accepted. However, the benefit of mammography has been shown to outweigh this risk. The value of mammography is exemplified by its superiority over any other method in detecting nonpalpable cancers that are still at a curable stage. The benefit becomes more pronounced when advanced techniques are employed which provide sharp images with minimal x-ray exposure.

X-ray units *dedicated* for mammography employ special compression devices and a molybdenum source for optimal visualization of breast tissues on film. The greater photoelectron effect of molybdenum over tungsten is due to the difference between the x-ray spectra of these targets, and yields enhanced contrast between fat, water density tissue and califications. A very tiny (microfocus) tungsten tube in a dedicated x-ray unit is also in use and promises comparable film quality. Increasing the source to image receptor distance and decreasing the target size further improves the resolution, allowing use of faster film-screen combinations with an even further reduction in dose. Improvements in these directions are continuing and should be encouraged.

Reduction of scatter has become one of the most important considerations in reduced dose mammography. One of the most direct ways to reduce scattered radiation is the use of aggressive compression of the breast. This is most effectively carried out with a dedicated mammographic unit. For optimal effect the compression should be carried to the point of discomfort. Obviously, encouragement and reassurance of the patient are desirable and the referring physician should be supportive of this procedure. Compression reduces the thickness of the breast with consequent reduction of dose. It provides a more homogeneous density throughout the breast and reduces motion and scattered radiation. All of this improves image quality.

The introduction in 1972 of single-emulsion high-detail film-screen combinations reduced the dosage of mammographic examinations by a factor of eight without sacrifice of diagnostic information. In 1975 a second generation of calcium tungstate screens for mammography resulted in 50 percent further dose reduction. More recently, rare-earth screens have been developed which provide greater x-ray-to-light conversion efficiency with an even greater reduction in dose.

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Radiology in Cases of Vertigo

VERTIGO is due to pathological lesions in the ear, posterior cranial fossa or cervical spine. The radiological techniques of computed brain tomography, complex motion tomography and posterior fossa myelography are extremely accurate in detecting the causes of vertigo. A thorough otological and neurological workup should be done before radiological examination is carried out. The indications and type of radiological examination for vertigo are determined by the clinical localization of the lesion.

Middle ear lesions causing vertigo include (1) labyrinthine fistula due to cholesteatoma or chronic otitis media; (2) temporal bone fractures; (3) perilymph fistula due to previous surgical operation or trauma to the ear. Complex motion tomography is the procedure of choice for these lesions.

Retrocochlear or internal auditory canal lesions include acoustic tumors, meningioma and epidermoids. Computed cranial tomography is the best technique for detecting lesions that extend from the canal into the cerebello-pontine angle cistern. Complex motion tomography and posterior fossa

myelography are necessary to detect lesions within the internal auditory canal.

Central lesions causing vertigo include cerebellar infarction, hemorrhage and tumors—both primary and metastatic. Isolated midline cerebeller lesions may only produce vertiginous symptoms that simulate peripheral ear lesions. These cerebellar lesions may only be detected on computed cranial tomography.

The adult Arnold Chiari malformation of the lower brain stem and upper cervical spine can result in vertigo. This malformation is best seen with posterior fossa myelography.

Sophisticated radiological techniques can detect many causes of vertigo. The selection of the proper technique is determined after a thorough neurological and otological examination.

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Evaluation of Seizure Disorders by Computed Tomography

MOST SEIZURE DISORDERS are *idiopathic* without discernible cause, such as tumor, vascular malformation or the like. In seizure disorders, plain radiography of the skull is very insensitive in the detection of intracranial pathologic conditions, and may be omitted in many cases. Electroencephalography is still helpful in the screening and detection of significant intracranial lesions, but nonspecific in etiological classification. Before the advent of computed tomography (CT), the radiographic evaluation of this entity was complicated, expensive and hazardous, often with a disappointing yield of pathologic findings. CT has simplified this evaluation, and has eliminated the need in many cases for other studies, especially pneumonencephalography. Although any epileptic patient may benefit from CT evaluation, the highest yield of intracranial abnormalities is shown in persons with a short duration of seizure activity at the time of examination (less than six months), advanced age (especially over the age of 65), focal neurological findings and focal seizure types secondarily generalized.

In general, 40 percent of CT scans evaluated in epileptic patients show abnormalities. Most changes are either diffuse or focal atrophy (61 percent of abnormalities). Neoplasms (10 percent), arteriovenous malformation (10 percent), infarcts (10 percent) and hydrocephalus (8 percent) are also shown.

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The Resurgence of Endocurietherapy

ENDOCURIE (interstitial or intracavitary implant) therapy employs radioactive isotopes placed close to or into malignant tissue. This approach creates certain physical and biologic advantages compared with external beam therapy. Implants may be temporary or permanent. When the tumor is anatomically accessible, temporary implants are usually (but not always) utilized; the patient remains in the hospital for the duration of the radioactive exposure, and all sources are removed before he is released. When the tumor is less accessible, permanent sources are placed at surgery. Until recently endocurietherapy had found its only major application in gynecologic malignancy, primarily because of the unsuitability of the commonly available radioisotopes (radium 226, cesium 137) for interstitial implants. More useful artificial isotopes have been developed recently, greatly expanding the clinical scope of endocurietherapy.

Iridium 192 is most useful for temporary implants. Unlike radium, which must be enveloped in a thick platinum jacket to contain gaseous radioactive daughter isotopes, iridium remains a solid and can be packaged in very small wires or seeds, providing source flexibility, minimizing tissue trauma and creating the possibility of *afterloading*. Afterloading is a procedure in which receptacles for the radioactive sources (small plastic tubes in the case of iridium) are placed into or near the tumor in the operating room; later in the isolation of a private hospital room, the radioactive sources are placed into these receptacles. Afterloading minimizes unnecessary personnel radioactive exposure.

Iodine 125, another manufactured isotope, has properties more suitable for permanent implants. Its wave energy, while biologically useful, is relatively low (28 kiloelectron volts), which means

that virtually all its radioactivity will be absorbed by the patient and almost no exposure to other people will occur. The sources are very small, thereby limiting normal tissue reaction, but are made radiopaque so that the radioactive dose may be calculated. Its relatively long half-life (60 days) is also advantageous for three reasons: (1) The seeds may be stored for several days before use without a severe loss of activity, facilitating clinical planning and scheduling; (2) radioactive exposure of tumor cells is protracted and at a low dose rate which may be biologically advantageous; (3) the intensity of radioactivity is relatively low, meaning that exposure to operating room personnel at seed insertion is minimal. The many advantages of this isotope have led to its increasing use and have rendered its predecessors (such as radon 222 and gold 198) obsolete.

With these isotopes in hand, intracavitary techniques are being extended to almost all solid tumors. Endocurietherapy will play an increasingly important role in clinical radiation oncology.

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EDITORIALS

Politics and Health Care Smoke Screens

SMOKE SCREENS are used to divert attention and to hide what is really going on from view. The technique is used on occasion by politicians and government leaders when they wish to draw attention away from what is really happening or when they simply do not wish to face up to what is obviously taking place. Since health care costs have been rising somewhat faster than other costs in the economy, the health care enterprise for some years now has been the target of all kinds of governmental criticism and at times even discriminatory abuse. The fact that this faster rise has occurred because both the amount and technical sophistication of the services rendered (both largely the result of earlier government initiatives) are far greater than ever before, is seldom if ever mentioned. Rather it has become fashionable to attack the health care enterprise as somehow a guilty party, a major cause of inflation, which therefore must be regulated and controlled as soon as possible. Politicians have touted health care costs as the number one concern of the public, which they are not, and have touted regulation as the only way to control health care costs, which it is not. The first tout is disproved by public opinion polls which do not show health care costs to be the number one concern of the public, and the second is disproved by the experience with the Nixon administration's discriminatory controls on medical costs which certainly did not solve the problem or have any long-term effect on the rising costs.

Health care smoke screens are now beginning to wear a little thin. Aside from the added costs of better access, major new advances and much improved technology—each considered to be good and desirable—health care costs are rising for the same reasons other costs are rising. And it does not take an economist to know that as more and more paper money is printed it becomes worth less and less, and that the wage price spirals, which occur in the health care enterprise just as everywhere else, increase costs without increasing productivity. In fact it seems that America is now determined and well on its way to pricing itself out of both the domestic and world markets largely for these reasons. The problems of health care costs seem almost insignificant when compared with the larger issues such as these, which have been behind health care smoke screens and hardly even discussed by government officials.

Perhaps fortunately, perhaps unfortunately, higher costs and uncontrolled inflation have reached the point where the nation may not now be able to afford the mounting costs of closer regulation of every detail of the health care enterprise. Having locked itself into ever-rising mandatory benefits to huge numbers of people, and ever-rising interest rates to an ever-growing national debt (among other things), the national government, in spite of its rhetoric, now seems to be backing off from a full-scale program of nationalized health care. Also there are signs that the high costs of health care are beginning to have something of a hollow ring to the public ear. Monetary inflation, rising food prices, and the availability and cost of gasoline affect just about everybody almost every day, and seem more important than health care costs to much if not most of the public.

Physicians can now do their bit to help dissipate the smoke screen by facing up more directly to some of the causes of public dissatisfaction with health care. Some of the costs are probably higher than they should be. These can be rooted out. More attention can be paid to the cost effectiveness of many medical care interventions. The voluntary cost containment programs espoused by the profession are beginning to do some of this. But there is also a need to pay more attention to what the public thinks of the medical profession and its role in health care. There is much

that is changing with respect to public attitudes toward medicine and the other professions, and these changes can be for better or for worse. They need to be understood, and influenced for the better where this is possible. And above all there is a need to show the public that the profession cares—cares about costs, cares about health and cares about people. We do a great deal of all of this now, but we could and should do more. We can do a lot more to help dissipate the health care smoke screens, and this would surely be good politics as well.

—MSMW

Interpreting Steroid Receptor Assays

THERE IS LITTLE QUESTION that estrogen and progesterone receptor determinations can substantially increase the accuracy of treatment regimens for patients with advanced breast cancer. However, noncritical acceptance of (and therapeutic decisions) based on findings from a single laboratory test may often result in disappointment; steroid receptor analyses on human breast tumors are no exception. In order to achieve maximal predictive accuracy, test results must be carefully interpreted in the biologic setting in which they have relevance. For this reason, it is of extreme value for clinicians to consider sources of noise in these assays; that is, explanations for observed responses to endocrine therapy in patients considered estrogen receptor (ER) negative and failure to obtain endocrine responses in patients termed ER positive.

The most common explanation for a so-called *false negative* result (tumor ER negative but patient responds to endocrine therapy) is laboratory error. Steroid receptors tend to be fragile proteins whose binding activity is pH and ionic strength dependent; in addition, they are thermolabile. Any number of errors in sample storage, handling or assay technique will convert an ER positive tumor to an apparently negative one. In a recent survey of approximately 65 laboratories doing ER assays, about a fourth of those responding incorrectly assessed ER concentrations in one or more of four standardized samples. (More than a third of laboratories failed to satisfactorily assess at least one of four samples for progesterone receptor.)

Most assays are made on cytoplasmic extracts. Previous exposure to endogenous hormone may have already caused receptor occupancy and subsequent nuclear translocation. In fact, recent data have suggested that in about 5 percent of tumors, receptor may be localized to the nucleus even in the absence of endogenous hormone. In either case a receptor containing tumor will be missed.

Heterogeneity of receptor content may exist at the microscopic or macroscopic level. That is, a tumor metastasis may be largely composed of non-receptor containing abnormal elements which dilute the receptor present in a few tumor cells. Alternatively, a biopsy specimen from a metastatic lesion may be ER negative while remaining sites in which response is assessed are ER positive. Inadvertently, a specimen submitted for ER assay may be either necrotic or adjacent to the actual tumor containing tissue. Falsely negative test results ensue.

Finally, a given endocrine therapy may be mediated via another receptor. For example, if an occasional patient with breast cancer responds to hypophysectomy because of a reduction in prolactin levels, and if expression of prolactin receptors were imperfectly linked to ER, then some ER negative tumors might respond to pituitary ablation.

While the overall response to endocrine therapy in ER negative patients is low (less than 10 percent in all major series) it is not zero, and these data point up the fact that no single laboratory test ought to be used to proscribe endocrine therapy forever in a given patient.

Far more frequently, patients are thought to have ER positive tumors but objective responses to endocrine therapy fail to materialize. A proper understanding of the setting in which this may occur can substantially improve the likelihood of success. First, so-called *false positive* results can arise through a variety of methodologic errors. It is unfortunately all too simple for poorly chosen assay techniques to fail to distinguish progesterone receptor from glucocorticoid receptor or corticosteroid binding globulin, and androgen or estrogen receptor from sex steroid binding globulin. Also, heterogeneity of cells within or between metastatic lesions with respect to binding activity may yield false positive results. That is, a tumor may contain sufficient ER to give a positive result but most of the cells may be ER negative and unresponsive. Alternatively, the assessed tumor nodule may be ER positive and hormone responsive but

different binding properties of other tumor sites result in a mixed or negative response to endocrine therapy. With respect to the former case (heterogeneity within tumors) one might expect there to be a positive relationship between concentration of ER and likelihood of endocrine response and this has been shown to be true in many series. Therefore, the predictive value of the test is considerably improved by quantitative assessment of ER concentrations.

There are many steps in steroid hormone action distal to the initial binding of the hormone to the receptor. Obviously, a defect in any one of these would result in an unresponsive tumor with apparently normal binding activity. An obvious solution to this problem is some assessment of the tumor response mechanism *in toto*. Elsewhere in this issue, Osborne and McGuire review the usefulness of the estrogen induced protein progesterone receptor in this regard.

It is illogical to expect that ER concentrations ought to predict response to a host of endocrine therapies, many of which (androgen or progestin administration, for example) may not be directly mediated by ER. Consequently, if a tumor lacks the receptor required for that therapy but contains ER a false positive result will be observed.

Finally, a tumor may in fact be hormone responsive, but the chosen therapy inadequate. For example, it is correct that responses to adrenalectomy are less frequent in patients who have not responded to oophorectomy; nonetheless, 10 percent to 15 percent of these patients will have objective responses to adrenalectomy. The latter therapy proves that these patients have hormone dependent tumors, but if they are assessed on the basis of the oophorectomy (which presumably was not able to sufficiently alter the hormonal milieu) the findings would not have been *false positive*.

Clearly, by knowing the site that was used for the ER assay, by being certain that the sample was transported and stored correctly, and by learning whether the assay methodology employed is valid, clinicians can vastly increase the odds in favor of getting helpful information. Given the cost of the assay, the necessity of a biopsy study and the amplified hazards of an incorrectly chosen therapy, it is highly appropriate for clinicians to demand that the assay laboratory prove the reliability of the assay by showing appropriate correlations with endocrine therapy in previous tests and by accurate results on unknown standards which are now available. With the large number of laboratories offering tests of dubious quality a caveat emptor attitude is surely warranted.

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Organized Medicine as 'My Doctors'

THERE ARE MILLIONS of people in this nation who have great confidence in the knowledge, integrity and skills of their own doctors but who are less sure of the integrity and skills of other people's doctors or of the medical profession as a whole. It is usually other people's doctors, and not "my doctor," who are perceived to be responsible for all the bad things they hear about doctors. Unfortunately organized medicine has become identified in the public consciousness more with other people's doctors than with "my doctors." Yet it is obvious that the medical profession is just as much made up of "my doctors" as it is of other people's doctors.

It would seem that the key is to be found in the doctor-patient relationship. The strength of a patient's confidence and trust in a physician seems to be more or less proportional to the strength of this relationship, but so far it has not been possible to project this to the relationship between the medical profession or organized medicine and the public or society as a whole. The fact is that medicine has been losing some ground in recent polls of public trust and esteem, although the profession still ranks relatively high and certainly above many if not most of its detractors. But the trend is negative and it should behoove the profession to begin to reverse it as quickly as possible.

It is suggested that the profession and organized medicine should try somehow to make the doctor-patient relationship come alive in the broader relationship between medicine and American society. A way to do this might be for physicians and organized medicine to become as visibly concerned with the health, quality of life and personal fulfillment of the individual person in today's society just as "my doctor" is concerned with

these things in dealing with the problems of each individual patient. Citizens, like patients, are persons each with a unique biological and experiential endowment. The special knowledge and skills of the profession as a whole, as well as the individual physician, naturally relate this personal uniqueness to such things as health, well-being, quality of life and even personal fulfillment. The tone and direction for such an organizational approach to a citizenry of unique persons, as distinct from an impersonal "public," will need to come from the profession's leadership, first through its councils and its spokesmen. Then the millions of doctor-patient contacts that occur in America each day can be used to bring the message home. Practicing physicians and organized medicine can espouse the problems of persons as individuals whether in patient care settings or in the broader context of society as a whole. In this way "my doctors" can become advocates and confidants of the people, focusing on their individuality and uniqueness rather than their sameness. And this can be important because it is the people—patients, families and friends—who will ultimately determine the future of medicine and the kind of care they will receive.

It surely is time that organized medicine becomes perceived as "my doctors" by the people of America rather than as other people's doctors, as is now too often the case. This should be possible to do if the effort is made.

—MSMW

CASE REPORTS

Refer to: Peirce TH, Yucht SC, Gorin AB, et al: Q fever pneumonitis: Diagnosis by transbronchoscopic lung biopsy. West J Med 130:453-455, May 1979

Q Fever Pneumonitis

Diagnosis by Transbronchoscopic Lung Biopsy

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Q FEVER, a rickettsial infection caused by Coxiella burnetii, has a worldwide distribution.[1] The organism has been recovered from a wide variety of animals and fowl.[2,3] Infection in man is caused by airborne organisms and in many cases is symptomless, with only a minority of patients requiring treatment.[4] However, it may present as a rapidly progressive fatal pneumonia[5] or as a chronic endocarditis with a mortality rate as high as 60 percent.[6]

The availability of specific antirickettsial drugs[7] emphasizes the importance of a specific diagnosis. However, serological tests or cultures will not provide a definitive diagnosis in less than seven to ten days and often may take longer.

We describe the case of a patient with fulminating Q fever pneumonia in whom the diagnosis was established early by lung biopsy, permitting specific treatment to be instituted promptly, with eventual recovery of the patient.

Report of a Case

A 26-year-old white man, an anthropology student, was admitted to the Sacramento Medical Center with a three-day history of pleuritic pain in the right side of the chest, dyspnea and a fever of 38°C (100.4°F). He worked in a primate center anatomy laboratory, collecting blood and saliva specimens from monkeys. In addition, he macerated tissue from various animals, such as birds, goats and raccoons, for the preparation of museum specimens. He was a nonsmoker.

Chronic ulcerative colitis had first been diagnosed 14 years previously and was well controlled with adrenocorticosteroids and salicylazosulfapyridine (Azulfidine) therapy. He had not used adrenal steroids in the previous 18 months. Two weeks before admission he had had a flare-up of his ulcerative colitis, which required hospital care for five days and subsided on treatment with salicylazosulfapyridine.

At time of admission, temperature and pulse rate were elevated and blood pressure was 90/60 mm of mercury. He was tachypneic, and the breath sounds were reduced at the right base with a pleural rub present in this area. There was some general abdominal tenderness without any organ enlargement.

Laboratory tests gave the following results. Hemoglobin was 12.4 grams per dl. Leukocyte count was 10,900 per cu mm with a normal differential, normal total eosinophil count and normal platelet count. Results of analysis of urine were within normal limits. Total serum protein was 6.5 grams per dl (albumin 2.1 grams), with slight elevations of the alkaline phosphatase and the serum glutamic oxaloacetic transaminase (SGOT) levels with the patient breathing room air, the arterial blood values were oxygen pressure (Pao_2), 71 mm of mercury; carbon dioxide pressure ($Paco_2$), 31 mm of mercury. The pH was 7.39. A roentgenogram of the chest showed some consolidation in the right lower lobe, with pleural fluid on the right.

Thoracentesis yielded 15 ml of blood-stained fluid with a protein content of 2.7 grams per dl, a glucose level of 110 mg per dl and a normal amylase level. The pleural-fluid lactic dehydrogenase (LDH) was 408 MU per ml with a simultaneously measured serum LDH of 700 MU per ml. All cultures of pleural fluid eventually gave negative results. Serum titers of antibodies to rickettsia, viruses and mycoplasma were measured.

During the 72 hours after admission, fever was higher and the patient noted severe frontal headache, increasing dyspnea and a generalized lym-

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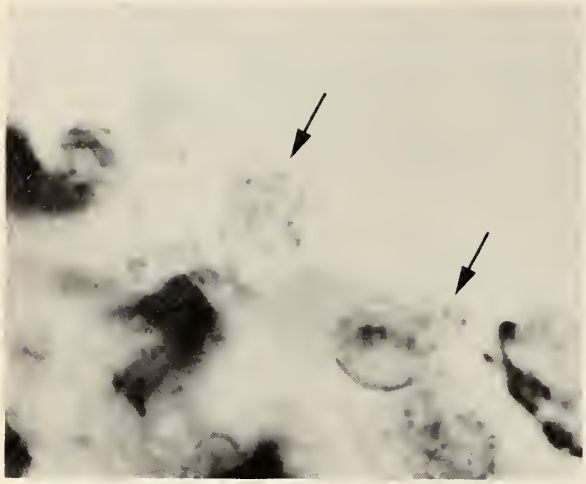

Figure 1.—Pulmonary tissue specimen obtained by transbronchoscopic biopsy, showing many alveolar macrophages, some of which contain intracytoplasmic inclusions **(arrows)** resembling coccobacillary bodies (hematoxylin-eosin stain, light microscopy, reduced from ×2,500).

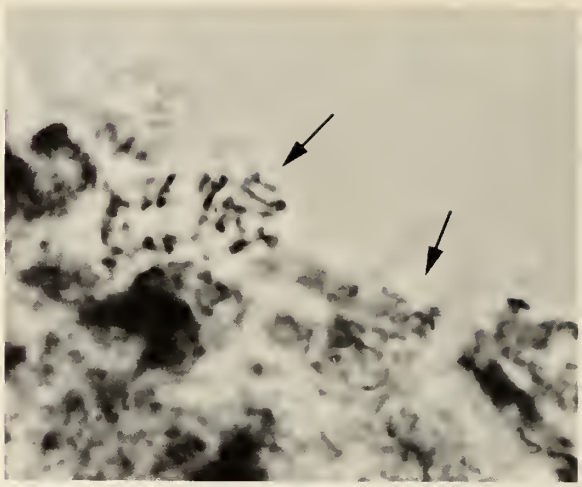

Figure 2.—Identical cells under phase contrast microscopy (reduced from ×2,500).

phadenopathy affecting the supraclavicular, axillary and inguinal areas. The liver and spleen were not enlarged. A lumbar puncture showed that cerebrospinal fluid was normal.

The pleural effusion on the right increased in size. A needle biopsy specimen from the pleura showed only fibrous tissue. A right axillary node biopsy specimen showed hyperplastic lymphoid tissue. Roentgenography of the chest at this time showed increasing consolidation in both lower lung fields. Respiratory status continued to deteriorate, and eventually Pao_2 was only 53 mm of mercury while the patient was breathing air enriched to 40 percent oxygen.

Three small pieces of lung tissue were taken from the left lower lobe through a fiberoptic bronchoscope with the transbronchoscopic biopsy technique. Following the procedure, a small pneumothorax developed which responded to closed intercostal drainage.

Sections of the lung biopsy material showed small coccobacillary bodies within the alveolar macrophages (Figures 1 and 2). Bronchial washings and brush biopsy material gave negative results on Gram stains and on cultures. Stains for Pneumocystis carinii were also negative.

Based on the lung biopsy and the clinical features, a provisional diagnosis of Q fever pneumonia was made, and therapy was started with chloramphenicol (750 mg four times a day). Mechanical ventilatory support was instituted. During the next ten days, temperature gradually decreased and the roentgenographic abnormalities and arterial blood gases showed steady improvement.

After 14 days, administration of chloramphenicol was discontinued; the patient's clinical condition then deteriorated rapidly again with increased fever, dyspnea, hepatic failure with jaundice, encephalopathy, tense ascites and an SGOT level of 800 units. Mechanical ventilation was reinstituted, and chloramphenicol therapy was resumed in a dosage of 3 grams per day; the patient's condition again improved. Because of leukopenia, the chloramphenicol was replaced after a week by doxycycline in a dosage of 200 mg per day. After two weeks, the dose was reduced to 100 mg a day and administration was continued for another two months. The ascites disappeared, and roentgenographic studies of the chest showed clearing of abnormalities. After three months, liver function returned completely to normal. On discharge from hospital (four months after admission), roentgenogram of the chest showed no abnormalities except for minimal scarring at the right lung base.

Serologic studies showed that the initial titer for Q fever was positive in a 1:8 dilution (complement fixation test for phase II antigen). Four weeks later, this test was positive in a 1:128 dilution; and, after six weeks, it was positive in a 1:256 dilution. Results of serologic tests for influenza, adenovirus, mycoplasma and psittacosis were negative. Titers for cytomegalovirus rose from an initial level of 1:8 to 1:128 dilution; this was considered to be probably due to multiple blood transfusions. Serologic titers for Coxsackie

B_5 virus were elevated in blood specimens drawn in both acute and convalescent stages; this probably resulted from a previous illness.

Evidence for the diagnosis of Q fever in this case includes the history of exposure, the compatible, clinical features, the presence of rickettsial-type organisms in lung biopsy specimens, the serological changes, the excellent initial response to therapy with chloramphenicol, the relapse when this was discontinued and the prompt response when use of the medication was resumed.

Discussion

As the clinical manifestations are frequently minimal, Q fever infection of the lungs probably occurs much more frequently than is generally recognized. In symptomatic cases, the clinical features commonly resemble viral or mycoplasmal infection.[7] It is unusual for the pulmonary involvement to be so widespread as to progress rapidly to respiratory failure. In addition to pneumonia, Q fever may cause pleural effusions, pericarditis,[8] endocarditis and hepatitis;[2] and it may give rise to acute exacerbations of chronic obstructive pulmonary disease.[9]

In most instances, a tentative diagnosis of Q fever can be made from the geographic and occupational features and a compatible clinical picture. For example, Q fever is endemic in the Davis and Sacramento areas in California,[10] and the knowledge of this circumstance helped arouse early suspicion of the presence of Q fever in this case.

Confirmation of the diagnosis of Q fever is usually accomplished by serologic or cultural techniques[6,11,12] that may require 10 to 14 days to complete. In fulminant cases, treatment for acute Q fever must be instituted before the diagnosis is positively confirmed. Although the disease responds to the administration of chloramphenicol and the tetracyclines, these drugs are only inhibitory, and clinical relapses are known to occur. For this reason, a minimum of three weeks of treatment following clinical resolution of the disease is recommended. The relapse in this case presumably reflected the early discontinuation of chloramphenicol therapy. The retreatment phase was continued for almost three months because of persistent low-grade fever and our fear that a second relapse might prove fatal to this severely debilitated patient.

Coxiella burnetii organisms within lung macrophages were first shown on an autopsy specimen in 1950.[13] There have since been several fatal cases in which rickettsial bodies could not be shown to be present in the lungs despite the presence of diffuse pneumonia.[7,14] The use of the Wolbach modification of the Giemsa stain and the Castaneda, Macchiavello and Goodpasture stains has been recommended to help identify the organisms within lung tissue.[5]

Transbronchoscopic lung biopsy utilizing the rigid or fiberoptic bronchoscope provides helpful diagnostic information in diffuse lung disease in up to 80 percent of cases.[15,16] As with any lung biopsy technique, there is some risk of morbidity and mortality.[17]

In fulminant cases of acute Q fever pneumonitis, where early institution of specific therapy is necessary to survival, the use of the transbronchoscopic lung biopsy technique to detect rickettsial bodies within lung macrophages can be extremely valuable. It is unlikely that the patient presented here would have survived had the diagnosis not been made in the acute stage of the disease.

Summary

A young man with a history of chronic ulcerative colitis presented with fever, progressive dyspnea, generalized lymphadenopathy, diffusely disseminated pulmonary consolidations and bilateral pleural effusions. A transbronchoscopic lung biopsy specimen from the left lower lobe showed rickettsial-type organisms within alveolar macrophages. A provisional diagnosis of Q fever was made, and this was later confirmed by serological methods. The patient recovered with specific antirickettsial therapy.

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Lindau Disease Treated by Bilateral Nephrectomy and Hemodialysis

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LINDAU DISEASE, also known as von Hippel-Lindau disease, is a hereditary disorder characterized by the association of cerebellar hemangioblastoma with any of several other visceral tumors.[1] These include retinal hemangioblastoma (the von Hippel tumor); spinal cord hemangioblastoma; pancreatic cysts; epididymal cysts and adenomas; pheochromocytoma, and renal angiomas, cysts, and carcinomas.[2] The diagnosis of Lindau disease depends on the demonstration of two hemangiomatous lesions in a single patient or the presence of a single lesion in a patient with a verified family history of the disease.

Renal cell carcinoma is present in approximately two thirds of patients affected with Lindau disease. It may be diagnosed clinically during life or appear as an incidental finding at autopsy.[2] Although Lindau originally believed that the renal tumors were always benign,[3] the metastatic potential of these neoplasms is now well documented.[4-6] Renal cell carcinoma is the cause of death in approximately a third of affected patients.[7] The typical tumor is multicentric in origin. An interval of several years may occur between resection of a hypernephroma in one kidney and the later appearance of tumor in the contralateral kidney.

Although a few patients with previous history of other types of renal malignancy have been accepted for dialysis,[8] little if any information is available regarding the suitability of patients with Lindau disease and renal carcinoma for hemodialysis. We present here the case of a patient with Lindau disease and bilateral renal carcinoma in whom bilateral nephrectomy and subsequent treatment with hemodialysis were carried out.

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Report of a Case

A 34-year-old white man was referred to San Francisco Veterans Administration Hospital in 1976 for evaluation of two months of increasing ataxia of gait. History showed that he had presented to another hospital in 1962 with similar symptoms and at that time had had resection of a cerebellar hemangioblastoma. Postoperatively he had had a persistent ataxic gait and weakness of the left arm and leg. His clinical status had remained unchanged for eight years when he again presented with increasing ataxia. Evaluation showed another cerebellar tumor which was felt to be unresectable. A course of treatment with radiation resulted in subsequent symptomatic improvement. He was again admitted to hospital two years later, when he presented after four weeks' experience of increasing headache, difficulty with vision and balance, and early morning nausea and vomiting. Bilateral carotid arteriograms showed a large cystic cerebellar lesion and two smaller cerebellar tumors. These tumors were excised, and the patient noted relief of his headaches, although the neurological deficits were unchanged.

His condition was then stable for the next three years, when the patient was again seen, this time with a two-week history of hematuria and right flank pain. On physical examination at that time, a palpable right kidney and an epididymal mass were discovered. An intravenous pyelogram showed a right renal mass and an arteriogram showed bilateral renal masses. During that period in hospital, excisional biopsy of the epididymal mass was accomplished, with a pathologic diagnosis of papillary cystadenoma. His symptoms resolved, and he was discharged. Two months later he was readmitted with a history of several days of hematuria and right flank pain. An intravenous pyelogram showed obstruction of the right ureter. The patient was observed and a follow-up pyelogram showed partial clearing of the obstruction, which at the time was attributed to the clot lysis. The patient's condition was then stable until the present admission.

Pertinent family history showed that the patient's mother had died at the age of 21 of a brain tumor.

On physical examination at the time of this admission, the patient was seen to be thin and had an obvious ataxic gait. Other neurological deficits included nystagmus on left lateral gaze, a slight weakness of the left upper and lower ex-

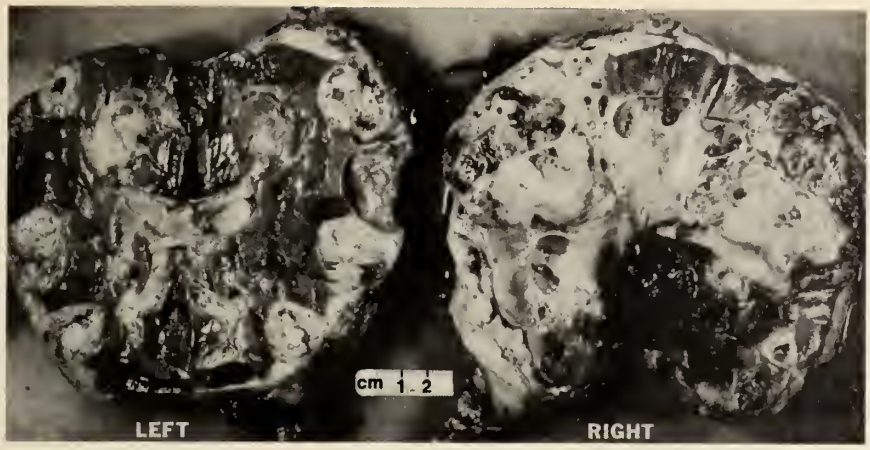

Figure 1.—Nephrectomy specimens from patient with Lindau disease and bilateral renal cell carcinoma. The left kidney has several foci of tumor, while the right kidney is extensively involved with malignant tissue.

tremities, and decreased sensation on the left side. Examination of the ocular fundi showed no evidence of retinal hemangiomata. On abdominal examination the right kidney was palpable. Laboratory values at time of admission included a hypochromic normocytic anemia with hematocrit of 28 percent. Serum erythropoietin level was 75 mU per ml (normal 7 to 36 mU per ml). An arteriogram showed bilateral renal masses, with extension of tumor into the right renal vein and inferior vena cava.

No evidence of distant metastatic disease was found after an extensive evaluation. A bilateral nephrectomy was done, including partial resection of the inferior vena cava. On pathologic examition of the kidneys (Figure 1), multiple bilateral renal carcinomas were found, with extension of tumor into the right renal vein and immediately adjacent portion of the vena cava. There was no indication that tumor extended through the renal capsule. Electron microscopy showed normal thickness of the glomerular basement membrane with no immune complex deposits.

Postoperatively regular hemodialysis was started. However, during the third hour of the second hemodialysis, the patient had a grand mal seizure. There was frequent recurrence of seizure activity during the next several days, with seizures occurring both late in dialysis and during the interdialytic period, before staff discovered that the patient had not actually been taking seizure medications. Thereafter, close supervision assured that he actually swallowed medications, and seizure activity ceased. Six months after initiation of hemodialysis three times a week, pericarditis developed, which responded promptly to treatment with indomethacin.

Seven months after initiation of hemodialysis, minimal ascites was observed on physical examination. Evaluation at that time included a paracentesis, with cytologic examination showing malignant cells. Cyclohexyl chlorethyl nitrosurea (CCNU) was then prescribed at 200 mg taken orally at intervals of six weeks, which he tolerated well. A year and a half after nephrectomy the patient is doing well on regular hemodialysis. He leads an active social life and participates in moderate activities, such as taking local sightseeing trips.

Discussion

This patient presented with many well-described manifestations of Lindau disease. The presenting symptoms of this entity are usually related to the cerebellar or retinal tumors[2] and may include headache, vertigo and emesis. Distinction is usually made between Lindau disease and Lindau tumor. "Lindau tumor" is used as an eponym for cerebellar hemangioblastoma, while "Lindau disease" is used for the association of this cerebellar tumor with visceral tumors. Cerebellar hemangioblastomas may account for 2 percent of all brain tumors and 7 percent of all posterior fossa tumors.[9] Such tumors represent a major source of early morbidity in patients with Lindau disease, often causing disabling neurological manifestations with occasional fatal complications.[1] Although these tumors are characteristically cystic with a mural nodule, a fourth to a third of them may be solid.

Although neurological manifestations are usually the major initial symptoms in Lindau disease, renal lesions are common and are a major cause of both morbidity and late mortality.[7] In one series of 11 patients with Lindau disease, nine had cysts or tumors (or both) involving the kid-

ney,[9] while in a series of several families with Lindau disease,[7] half of the patients with renal cell carcinoma had metastatic disease. Renal cell carcinoma associated with Lindau disease appears to differ somewhat from sporadic hypernephroma in the earlier age at diagnosis, the tendency toward multicentric origin and the lack of male predominance.

There is no available information about a possible increased incidence of neurological complications of dialysis in those patients with a previous history of resected cerebellar tumors. Complications in this group of patients might include an increased incidence of either dialysis disequilibrium syndrome with seizures or intracerebral bleeding, the latter due to repeated heparin administration required for hemodialysis. In the case reported here, the initial seizures may have been a manifestation of dialysis disequilibrium syndrome, but they also may have been due, at least in part, to failure to take seizure medication. He has been seizure-free since this was corrected and there has been no clinical evidence of intracerebral bleeding after more than a year and a half of regular hemodialysis. This patient has had no unusual complications of hemodialysis due to the preexisting cerebellar tumors and neurosurgical procedures. Based on this information, we believe that patients with Lindau disease and bilateral renal carcinoma should be considered as candidates for hemodialysis. However, it is imperative that this decision be made early in order to avoid the more extensive morbidity of metastatic disease.

Renal cell carcinoma is among the leading causes of death in patients with Lindau disease.[7] Improvement in prognosis of patients with Lindau disease and renal cell carcinoma will depend on earlier detection and treatment of the several treatable manifestations of this disease. Christoferson and coworkers[10] studied 90 members of an affected family and noted a 12 percent incidence of the combination of cystic and angiomatous lesions. They suggested that the trait is inherited in a modified dominant pattern with incomplete penetrance. Silver and Providence[11] reported an even higher incidence (80 percent to 90 percent penetrance) in a retrospective study of a large affected family.

Melmon and Rosen[2] advocated screening of affected kindreds. Removal of hemangioblastomas from the central nervous system, detection and treatment of retinal hemangioblastomas before visual acuity is decreased, and genetic counseling are reasonable steps to decrease morbidity in this disease. In addition, renal cell carcinoma associated with Lindau disease should be excised early before complications due to metastatic disease can occur.

With earlier diagnosis and improved methods of treatment of the cerebellar tumors in this disease, it is likely that more patients will survive long enough for renal carcinomas to develop. These renal tumors will often ultimately be bilateral and, therefore, a decision will be required as to suitability of the patient as a hemodialysis candidate.

Summary

A 34-year-old man presented with several manifestations of Lindau disease, including bilateral renal cell carcinomas. He also had a previous history of neurosurgical procedures and radiation therapy for recurrent cerebellar tumors. A bilateral nephrectomy was done, and the patient was placed on regular hemodialysis. He has had no unusual complications of hemodialysis during a year and a half of treatments three times each week. Although the initial symptoms of Lindau disease are usually due to cerebellar tumors, renal cell carcinoma is often a major cause of late morbidity. With improved treatment of the cerebellar tumors, it is likely that more patients with Lindau disease will survive and that renal carcinoma will develop subsequently. Patients with Lindau disease and bilateral renal cell carcinoma should be considered as hemodialysis candidates. This decision should be made early before metastasis has occurred.

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Refer to: Browne PM: Rhabdomyolysis and myoglobinuria associated with acute water intoxication. West J Med 130: 459-461, May 1979

Rhabdomyolysis and Myoglobinuria Associated With Acute Water Intoxication

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RHABDOMYOLYSIS AND MYOGLOBINURIA have been associated with variety of syndromes and clinical situations. Classification based on etiology is usually divided into hereditary and sporadic.[1,2] The most common cause of rhabdomyolysis is physical injury to skeletal muscle resulting from exertion or crushing. Common clinical settings include "squat-jump" and related syndromes, convulsions, compression of the body in prolonged coma and ischemia resulting from arterial occlusion. Metabolic causes are somewhat less common and include alcoholism, barbiturate use, nonketotic hyperglycemic hyperosmolar coma, heat cramps and chronic hypokalemia. More recently, rhabdomyolysis has been recognized as a complication of parathyroidectomy and calcium supplementation.[3]

We are reporting a case of rhabdomyolysis and myoglobinuria which was associated with acute water intoxication in an otherwise healthy man.

Report of a Case

A 62-year-old man was admitted to hospital because he was lethargic and confused. He was in good health until one day before admission, when he began drinking a great deal of water. The patient thought that his urine output was too low and tried to remedy this by drinking more fluid. There was no record of the total amount of fluid that the man drank; however, his wife estimated that he had drunk 1 to 2 quarts per hour for eight to ten hours. He became lethargic and confused. At 3 AM paramedics were summoned and he was admitted to hospital.

Two months before admission the results of the patient's annual physical examination were normal except for an inguinal hernia. He took no medications. Activity during the day was limited to light housework. There was no history of renal or endocrine disorders. Physical examination showed blood pressure of 100/50 mm of mercury, a pulse of 64 beats per minute, a temperature of 38.3°C (101°F). The skin turgor was normal. The pupils were the same size and reacted normally to direct light. Results of funduscopic examination were normal with no papilledema. The ears, nose and throat were normal. The neck was supple with no indication of jugular venous distention. The chest was clear to auscultation and percussion. Results of cardiac examination were normal. The abdomen was soft with no organomegaly, although a left inguinal hernia was noted. The prostate was minimally enlarged with no indication of nodules. The extremities were without edema. There was no appreciable muscle swelling or tenderness. Reflexes were active in the ankles, quadriceps and biceps. The peripheral pulses were normal.

The findings of laboratory studies are shown in Table 1. Additional studies carried out the first day in the hospital showed the following: serum osmolality, 242 mOsm per kg, with urine osmolality of 45 mOsm per kg; spot urine sodium, 40 mEq per liter; urine potassium, 99 mEq per liter; urine myoglobin, 38 to 75 mg per liter (differentiation from hemoglobin by counterimmunoelectrophoresis technique, Bioscience Laboratory, Van Nuys, California).

The initial creatinine phosphokinase (CPK) value was 1,014 IU per liter (100 percent MM fraction) and within 36 hours it was 98,000 IU per liter (100 percent MM fraction). Other findings were as follows: serum calcium, 8.0 mg per dl; phosphorus, 2.4 mg per dl; glucose, 110 mg per dl; blood urea nitrogen, 4 mg per dl; creatinine, 0.7 mg per dl; uric acid, 3.1 mg per dl; cholesterol, 173 mg per dl; total protein, 6.1 grams per dl; albumin, 3.6 grams per dl; total bilirubin, 1.6 mg per dl; alkaline phosphatase, 42 units per liter; lactate dehydrogenase, 725 Wacker units; serum glutamic oxaloacetic transaminase, 500 units; globulin, 2.5 grams per dl.

Lumbar puncture yielded clear fluid with a glucose value of 86 mg per dl, protein of 41 mg per dl, five red blood cells and two polymorphonuclear neutrophils per cu mm.

An electrocardiogram showed a first degree atrioventricular block which returned to normal by the third day in the hospital. A roentgenogram of

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the chest showed no abnormalities. Arterial blood gas studies, with the patient breathing room air, showed an arterial oxygen pressure of 64, an arterial carbon dioxide pressure of 34, pH of 7.48 and a bicarbonate value of 25 mEq per liter.

Hospital Course

Fluid intake was restricted and sodium bicarbonate was given to alkalinize the urine. The urine pH was maintained above 7.0. Urine output exceeded fluid intake for the first 48 hours. Diazepam was used for sedation. The serum electrolytes returned to normal levels within 48 hours although the CPK remained greatly elevated. Mental status improved quickly and was normal at the time of hospital discharge. Renal function remained normal. Urine color turned to hazy, red-orange after 24 hours but was free from myoglobin by the fourth hospital day. Hemoglobin level remained stable.

The patient was seen one month after discharge; mental status was normal, as well as hemoglobin level, serum enzymes, renal function and findings on analysis of urine.

Discussion

There are several known causes of myoglobinuria that should be considered in reference to this case. Hypokalemia has been associated with rhabdomyolysis and myoglobinuria. Whether hypokalemia by itself is a cause of rhabdomyolysis remains a debatable point. In many of the earlier reported cases linking hypokalemia and rhabdomyolysis, patients were receiving medication that may have had some direct myotoxicity. In a case reported by Heitzman,[4] steroids were used in a patient who had regional enteritis and in whom severe hypokalemia and myoglobinuria developed during treatment. Other patients with rhabdomyolysis associated with hypokalemia were receiving such medications as glycyrrhetic acid, carbenoxolone sodium and amphotericin B.[5-7] In another instance rhabdomyolysis was associated with hypokalemia of renal tubular acidosis.[8] Our patient was receiving no medications and was not acidotic. The question of isolated hypokalemia causing rhabdomyolysis is still not settled, but in most cases where the major metabolic derangement is hypokalemia the serum potassium is severely reduced, often below 2.0 mEq per liter. Our patient's lowest recorded value of 3.0 mEq per liter, although abnormal, is not uncommon and is not a cause of rhabdomyolysis.

Hyponatremia accounts for the confusion and lethargy but is not known to be a cause of rhabdomyolysis by itself. In many reported cases of abnormal metabolic states, hyponatremia is one of several abnormalities. The degree of hyponatremia in this case, while abnormal, is not uncommon in clinical medicine. The use of diuretic medication, syndromes of unusual antidiuretic hormone secretion, acute and chronic dilutional states, essential hyponatremia and hyponatremic dehydration are among the more common situations. Acute psychogenic polydipsia as a cause of hyponatremia is not rare. Rhabdomyolysis is not associated with these hyponatremic conditions.

Several laboratory values were absent. Hyperuricemia, hyperkalemia, and hyperphosphatemia are often seen with rhabdomyolysis but were not observed in this case. The overall dilutional state present in the patient on admission is adequate explanation for lack of these abnormalities early in the course of the illness, and the preservation

TABLE 1.—*Findings of Laboratory Studies*

Date, Time	Serum Sodium mEq/L	Serum Potassium mEq/L	BUN, mg/dl	CPK	SGOT U/L	LDH U/L	Hbg gm/dl	WBC 10^3/cumm	Urinalysis							
									pH	Specific Gravity	Occult Blood	Color	Glucose	Protein	RBC	Myoglobin mg/L
8/21, 3 AM	116	3.0	5	1,014	42	150	..	..	..	..	..	..	..	..	..	..
8/21, 9 AM	119	3.7	..	..	..	..	12.4	8.0	5.5	1.001	3+	pink	neg.	1+	2-4	38-75
8/21, 6 PM	120	3.5	..	..	..	..	13.3	8.4	7.5	1.005	3+	red orange	neg.	4+	25-35	..
8/22, 9 AM	126	3.5	6	78,000	720	2,630	..	..	..	..	..	..	..	..	..	..
8/22, 6 PM	132	3.6	5	98,000	..	..	..	..	..	..	..	..	..	..	..	..
8/23	138	4.0	4	89,000	1,115	2,010	..	..	..	..	..	..	..	..	..	..
8/24	139	4.2	7	44,600	..	..	13.8	7.2	7.0	1.044	3+	yellow	trace	neg.	5-10	..
8/25	135	3.8	9	39,000	..	..	..	..	..	..	..	..	..	..	..	neg.
8/26	135	4.7	13	14,200	..	..	..	..	..	..	..	..	..	..	..	..

BUN = blood urea nitrogen
CPK = creatinine phosphokinase
SGOT = serum glutamic oxaloacetic transaminase
LDH = lactic dehydrogenase
Hbg = hemoglobin
WBC = white blood cells
RBC = red blood cells

of normal renal function during the hospital course prevented the appearance of hyperuricemia, hyperkalemia and hyperphosphatemia.

The high spot urine potassium value in the presence of hypokalemia seems to account for the renal excretion of potassium preventing hyperkalemia.

Exertion, especially in a warm environment, is a common cause of rhabdomyolysis.[9] The patient was admitted to hospital on a warm August day with temperatures reaching 93°F. However, the patient's exertion was not unusually excessive; household chores such as cleaning and cooking, and light yard work were all that were decribed. As the patient's mental status became abnormal, some agitation and confusion were noted. Administration of diazepam was required in the hospital because of the patient's repeated attempts to climb out of bed. However, documentation of a convulsive episode was not present.

The causes of psychogenic polydipsia are poorly understood. Many patients are severely disturbed, even psychotic. However, anxiety may be the only psychological disturbance evident. How this emotional state severely alters thirst is unknown. Our patient was scheduled to be admitted to another hospital for elective repair of an inguinal hernia the same day that the acute water intoxication developed. The patient later freely admitted feeling anxiety about this surgical procedure.

It seems likely that the cause of the observed rhabdomyolysis and myoglobinuria was multifactorial. In the metabolic setting of acute hypokalemia and hyponatremia, exertion (agitated behavior) and temperature elevation were enough to cause muscle cell injury and release of myoglobin. Fortunately, renal failure did not occur and conservative measures such as sedation, fluid restriction and alkalinization of the urine were all that were necessary.[10]

Summary

Rhabdomyolysis and myoglobinuria were observed in an otherwise healthy 62-year-old man following acute water intoxication. Pronounced hyponatremia and hypokalemia were present on admission. Various possible causes of rhabdomyolysis including hypokalemia, hyponatremia and exertion are discussed.

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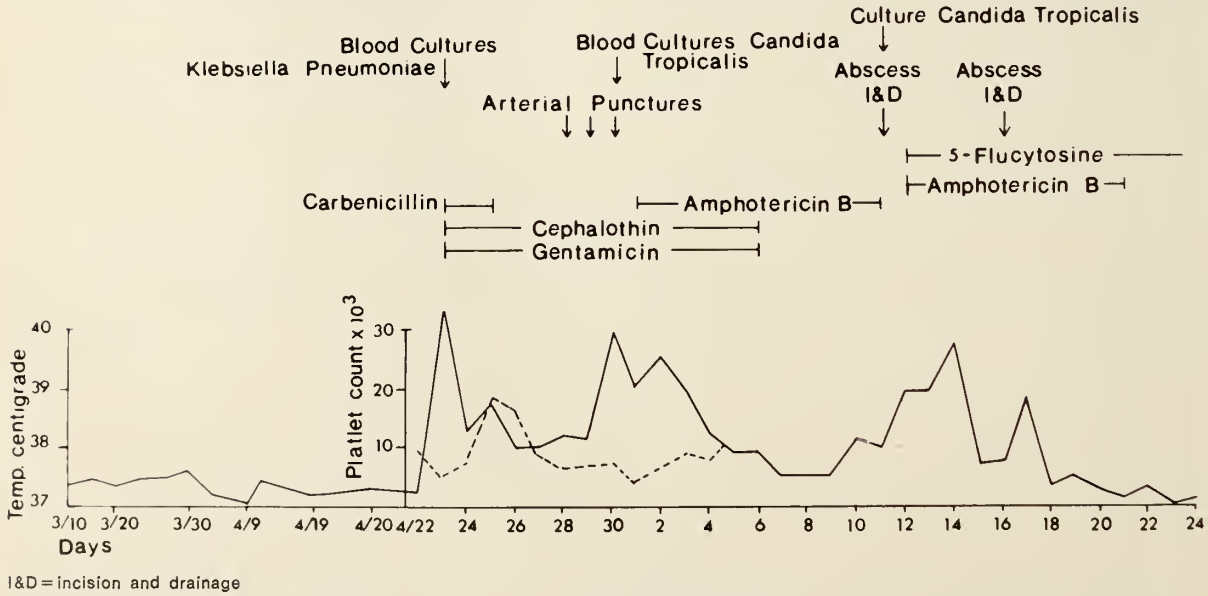
Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Candida tropicalis Abscess Following Arterial Puncture

TO THE EDITOR: Although arterial peripheral blood gas (ABG) determinations are routinely used in the management of complicated medical and surgical cases, and are rarely associated with problems, we wish to report a significant case of severe Candida tropicalis abscess formation secondary to arterial puncture.

A 25-year-old woman with acute lymphocytic leukemia was initially treated unsuccessfully with vincristine (2 mg per week for four weeks) and prednisone (110 mg per day). Remission occurred with a second course of treatment consisting of daunomycin (120 mg per day for three days), cytosine arabinoside (175 mg twice a day for nine days), thioguanine (175 mg twice a day for nine days) and prednisone (110 mg per day). Subsequently a small bowel obstruction with bloody diarrhea, a temperature of 40°C (104°F) and hypotension developed. Intravenous therapy with carbenicillin, cephalothin and gentamicin was initiated and the patient's fever abated in 48 hours; Klebsiella pneumoniae were obtained from cultured blood specimens. Fever recurred in 48 hours and multiple blood specimens grew pure cultures of Candida tropicalis even after removal of all indwelling venous catheters. The patient was treated with amphotericin B (136 mg per day for ten days). During the second febrile episode three ABG specimens were obtained, two from the patient's left radial artery and one from the right brachial artery; the patient was also leukopenic, thrombocytopenic (platelets, 5,000 to 8,000 per cu mm) and had an abnormal coagulation profile. Four days later the peripheral leukocyte count had recovered (leukocytes, 2,100 per μl, with 85 percent polymorphonuclear neutrophils) and at that time she complained of pain and swelling at the site of a previous puncture of the right brachial artery. During the following week a frank abscess developed at that site and upon incision 400 ml of purulent material was obtained, with yeast formations visible on microscopic examination



I&D = incision and drainage

Figure 1.—Clinical course of patient in whom Candida tropicalis abscess developed after arterial punctures.

and subsequently identified on culture as Candida tropicalis. A small abscess noted on the patient's left wrist at the site of another arterial puncture was also drained and the fluid produced no growth on culture. The patient was treated for ten days with a combination of amphotericin B and flucytosine, resulting in the resolution of fungemia and healing of the abscess cavities. The clinical course of this patient is shown in Figure 1.

Arterial blood gas determinations are frequently necessary in critically ill patients and usually do not cause complications. Petty and co-workers[1] reported 475 arterial punctures without complications in 54 patients. Fleming and Bowen[2] found in their series of more than 4,000 ABG determinations that hematoma formation was the most common complication with an incidence of only 0.58 percent, and that there were no serious sequelae from this mild complication. The risk of hematoma formation and its consequences appears to increase in patients receiving anticoagulant therapy. Neviaser and associates[3] reported that in 13 patients hematomas developed following femoral or brachial artery punctures while the patients were receiving therapeutic doses of heparin. Luce and co-workers[4] similarly reported that in seven patients receiving anticoagulant therapy compressive neuropathy developed secondary to hematoma formation from brachial artery punctures; they felt that the radial artery was the preferred site for ABG sampling in patients receiving anticoagulant therapy.

Infection of a hematoma is a recognized surgical complication and Neviaser[3] reported two cases in his series. He did not describe the results of Gram stains or cultures; however, he did note that primary therapy was incision and drainage. The occurrence of a Candida tropicalis abscess in our patient is unusual but not surprising. It has been shown that patients with hematologic malignancies or immune suppression have a greater risk of significant fungal infection. Also, hematoma infections with Candida species have been noted in surgical patients. We believe this is the first time that Candida tropicalis has been associated with an abscess following arterial puncture for ABG determinations.

This observation shows that even the simplest of invasive procedures can be associated with a risk. It should also be stressed that these risks are magnified in patients receiving anticoagulant therapy who have immunologic disorders secondary to their underlying illness or chemotherapy. To minimize the risk of hematoma formation and its sequelae, we recommend that ABG samples should not be obtained from brachial or femoral artery sites. We also feel that patients should be observed for evidence of abscess formations if arterial punctures are done during a period of septicemia.

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Hypertrophic Cardiomyopathies

TO THE EDITOR: We would like to comment on Dr. J. Michael Criley's interesting editorial remarks in the April issue (Criley JM: The bottom line syndrome—Hypertrophic cardiomyopathy [Editorial Comment] West J Med 130:350-353, Apr 1979) concerning our review of hypertrophic cardiomyopathy (Ross J Jr, Shabetai R, Curtis G, et al: Nonobstructive and obstructive hypertrophic cardiomyopathies—UCSD School of Medicine and San Diego VA Medical Center [Specialty Conference]. West J Med 130:325-349, Apr 1979), which appeared in the same issue. We acknowledge here, as we did there, his important contributions to the understanding of the pathophysiology of the hypertrophic cardiomyopathies.

It is hoped that we succeeded in making clear to our readers that we do not consider outflow tract obstruction to be the "bottom line" in hypertrophic cardiomyopathy. We emphasized that a systolic pressure gradient frequently is absent and when present is variable and unrelated to prognosis or symptoms; moreover, the mechanisms of its genesis and its abolition by myectomy are still not understood. Our preference for the term *hypertrophic cardiomyopathy* over the term hypertrophic subaortic stenosis indicates our belief that this is a disease of heart muscle, albeit mainly of the ventricular septum, and we agree that the disorder may create major disturbances in the diastolic as well as the systolic function of the heart. Thus, to state that left ventricular outflow tract

obstruction exists in some cases of hypertrophic cardiomyopathy is *not* to state that outflow tract obstruction is necessarily the predominant hemodynamic fault in an individual case, nor does this statement imply that obstruction develops before a substantial amount of left ventricular ejection has occurred. In fact, in patients with systolic pressure gradients left ventricular contraction can be unobstructed early in systole, obstructed in midsystole and isovolumetric in late systole[1]—a view shared by Wigle in a recent editorial.[2]

In summary, we—together with probably the great majority of investigators in this field—believe that left ventricular outflow tract obstruction can occur in hypertrophic cardiomyopathy, although it is only one of several hemodynamic manifestations that may characterize this fascinating disorder. We fear that by resurrecting this long defunct controversy, Dr. Criley may spread the very confusion he rightly seeks to dispel.

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Comment on 'Sears Suit'

To the Editor: I was shocked and dismayed to read the editorial in the March 1979 issue, stating "Sears Roebuck and Company is to be commended for applying a little heat to this iceberg [governmental laws, rules and regulations] and it is to be hoped that in time, and perhaps with more heat, the iceberg itself can be reduced to more manageable size." I think your naiveté is showing. To many responsible people, the Sears suit appears to be nothing more than a smoke screen for Sears' continuing employment practices which discriminate against the promotion of women and for Sears' avoiding payment of penalties for discriminating employment practices.

If we doctors want to participate in improving governmental function and efficiency, it seems clear to me that commending what Sears is doing has little to do with the matter. How about if a state or national medical association were to aggressively support the efforts of the Institute for the Study of Democratic Institutions for the modernization of our United States constitution? Now efforts in that direction might really help to lessen government red tape while at the same time preserve the spirit of our Bill of Rights which holds that all men and women should have an equal chance to better themselves in America.

GLEN G. CAYLER, MD
Sacramento, California

We seem to differ on the means but agree on the ends.

—MSMW

More on Cumulative Injury

To the Editor: My name was mentioned rather prominently in several recent letters to the editor concerning cumulative injury (February 1979 issue), in connection with my letter in the December 1978 issue. I would like the opportunity to reply.

Dr. Franklin Drucker made a number of comments, several of which take observations of mine out of context, and he offers no concrete suggestions as to how to improve the system. First, I would like to reply to his remark that I am unwilling "to recognize that stress and strain contribute to human misery and disability." I am in full-time practice of internal medicine and have been for 25 years. I am sure I have seen and treated as much misery and disability as Dr. Drucker. The point in my previous letter was that in the types of ailments that I am asked to evaluate—primarily hypertension, angina, myocardial infarctions and other degenerative ailments—there is simply no medical evidence that these conditions are caused or aggravated by the types of stresses and strains patients indicate are present in their work environment.

If we wish to make illness and disability a system of social justice, and compensate without regard to causation, fine, so be it. But if we wish to compensate those truly injured or disabled as a result of their occupation, then there should be concrete medical evidence that such is indeed the case.

In my review and evaluation of patients, if I

feel there is an industrial relationship or *may* be, I always indicate this in my report, and I have never been questioned by a lawyer or an insurance company, or asked to change my opinion.

Dr. Drucker suggests that a panel of medical experts is not the answer, and indicates that the courts have found this approach does not work. My response is that these problems are medical problems and no one is more qualified to make these decisions than a panel of medical experts specialized in the particular field. I am sure that if Dr. Drucker develops chest pain he will call his doctor and not his lawyer. As I stated in my previous communication, if the panel cannot come to an agreement as to an industrial relationship or lack of same (I feel a small minority will end thusly), the legal process can supervene. When the legal process is, as is the case now, instituted from the beginning, it is long and costly, and each side in effect cancels the other out. In my experience, when there is evidence of injury the insurance companies make no complaints about settling.

Admittedly the solution is not perfect and clearly the causes of many medical ailments are multifactorial and obscure, but I believe these medical problems should be settled by medical experts and not lawyers who are trained to represent their clients in the best possible light, rather than seek the truth.

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Carnation Instant Breakfast

To the Editor: The purpose of this letter is to call attention to some errors regarding Carnation Instant Breakfast (CIB) that were reported in Table 2 of the article entitled "The Challenge of Nutritional Maintenance in Cancer Patients" in the February 1979 issue.

The normal dilution of our product should be one package of CIB mixed with 240 ml of whole milk, *not water*. Also, the product has undergone an instantizing process, eliminating the need to be mixed in a blender as stated in the table. Regarding the nutritional composition, CIB mixed with whole milk should provide 1,055 kilocalories and 132 grams of carbohydrate per liter rather than 967 kcal and 117 grams as shown. The values for protein and fat were correct.

We also would like to point out that the column in Table 2 showing price per ounce is misleading. It would be better to do a price comparison of the products in the same physical form. For example, although one dry ounce of CIB powder does cost $0.17 as listed, one fluid ounce of CIB mixed with whole milk (which is the form the patient would be consuming) would cost only $0.03, assuming a half gallon of whole milk costs $0.70. The cost figures as they appear in Table 2 make it seem as though the dry products are more expensive than the liquid canned products, which is incorrect in some cases.

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Charges for Emergency Services

To the Editor: We would like to underscore a point raised in a recent article and editorial (Allen and Teufel's "Organization of Emergency Services" and Schroeder's "The Increasing Use of Emergency Services—Why Has It Occurred? Is It a Problem?" in the January 1979 issue) regarding the high cost of emergency medical services. A concern was expressed that present emergency rooms are not ideal trauma centers and fall short when assessed against other alternatives for nonemergency services.

As is universally recognized, emergency rooms are often utilized for services that could be rendered more efficiently in another setting. We are particularly concerned about the cost of these services as compared with those for visits to private physicians. We surveyed 456 consecutive charges for visits to private physicians for the diagnosis of tonsillitis, pharyngitis or upper respiratory infection. The average charge, *not* including laboratory or x-ray studies, for these diagnoses breaks down as shown in Table 1.

In addition, we obtained the average charge for these diagnoses for 25 patient visits to a local hospital's drop-in clinic—$19.00—and for 30 patient visits to a local emergency room—$47.00. However, these latter two had a higher percentage of new patient visits and thus are not strictly comparable with the private physician data.

In an effort to look at the reasons for the difference in charges between different specialties we looked at the distribution of RVS (Relative Value Studies) numbers used. The mode (the number used with the highest frequency) was Established

TABLE 1.—*Average Charges for Diagnosis of Tonsillitis, Pharyngitis or Upper Respiratory Infection*

		Number of patients
General practitioners	$15.03	211
Family physicians	15.19	56
Pediatricians	15.48	152
Internists	16.06	23
Ear, nose and throat physicians	22.60	14

Limited for the pediatricians, internists and ear, nose and throat specialists, and Established Brief for the general or family practitioners. The number of new patients did not explain the differences and was under 20 percent for all specialists.

The least expensive visit for handling tonsillitis, pharyngitis or an upper respiratory infection is with private general or family practitioners, and this is a third the cost of a visit to an emergency room in our area. We expect comparable data are available in many locales. A family physician's private office seems the ideal place to care for patients with these illnesses.

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Rehabilitation Through Marathon Running

TO THE EDITOR: Schroeder and Wagner[1] have reported in this journal encouraging follow-up statistics on 81 patients with cardiac disease who have completed the 42-km Honolulu Marathon. This event has a medically supervised (noncompetitive) division for rehabilitated cardiac patients and wheelchair athletes at present. They are thinking of adding a "diabetic division" and a "chronic lung disease division" in the future. Interested physicians or their patients can write to J. A. Schroeder and J. O. Wagner, Cardiac Rehabilitation Program, Central Branch YMCA, 401 Atkinson Drive, Honolulu, Hawaii 96814.

In the course of running some 100 marathons myself, I have compiled a list of 131 marathoners with cardiac disease including 48 with previous myocardial infarction and 19 who have had coronary-bypass operations. Follow-up shows that 126 are alive and running after 500 patient-years. Of the five who have died, only one showed progressive atherosclerosis at autopsy (Figure 1). This elderly man continued to chew tobacco and *swallowed all the juice* from three boxes of chewing tobacco a week. The plaques were very inflamed. This suggests that tobacco juice contains highly angiotoxic material.

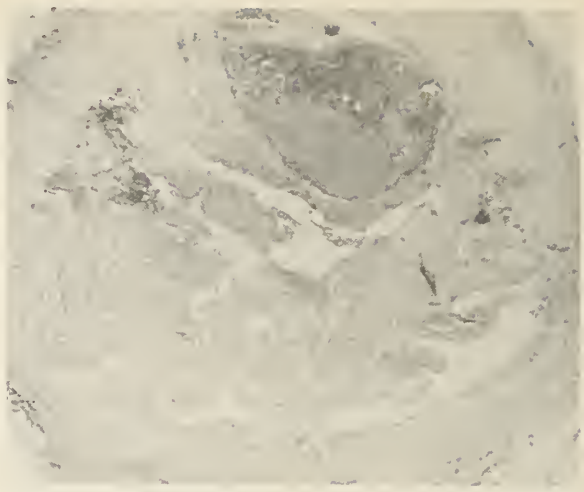

Figure 1.—Marathon runner's coronary artery showing atherosclerosis and thrombosis. This man, in his mid-60's, chewed tobacco and swallowed all the juice. The pronounced inflammation is attributed to the angiotoxic material in tobacco juice. (H & E stain; reduced from X 10)

Rehabilitation programs in Canada and the United States have been using marathon training as a tool for risk-factor modification for almost ten years. Six institutions have cooperated with my forensic surveillance over those athletes with cardiac disease who have reached the 42-km marathon distance. I have been very encouraged by the results.

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Theophylline Toxicity

TO THE EDITOR: Recent reports on the frequency and severity of the toxic effects of theophylline in obese patients or those with hepatic cirrhosis, chronic lung disease or congestive heart failure, have shown a high morbidity in cases where the serum level exceeds 50 μg per ml—roughly twice the therapeutic level.[1-5] Optimism concerning the prognosis in these cases has been generated by

recent advances in charcoal-column hemoperfusion.[6] A case of survival in massive theophylline overdose shows the gamut of clinical events that characterize the toxicity of this pharmacologic agent.

A 51-year-old 93-kg (205-pound) woman with a history of asthma and chronic schizophrenia ingested a "bottle of Tedral" (a combination of theophylline, ephedrine hydrochloride and phenobarbital) because of insomnia and presented within hours to the emergency unit because of severe agitation. On examination the patient was noted to be restless, tachypneic and obese, with cool, diaphoretic skin, slurred speech and vertical nystagmus. Pupils were 6 mm and sluggishly reactive. Rectal temperature was 35.5°C (95.9°F), pulse 140 and regular, blood pressure 100/60 mm of mercury, and respirations 24 and somewhat labored. Bilateral wheezing and thick, yellow secretions were present. Attempts to give charcoal orally were resisted. While under observation the patient became hypotensive (blood pressure 60/0 mm of mercury). Cardiac monitoring showed an irregular supraventricular tachycardia; acidosis and hypokalemia were present. After the intravenous administration of fluids and potassium chloride, arterial and central venous pressures returned to normal ranges. Approximately 12 hours after drug ingestion a grand mal seizure occurred, accompanied by pronounced bradycardia and hypotension; serum theophylline level was 148 μg per ml. After two hours of persistent seizure activity, pancuronium bromide (Pavulon) was given. Creatine phosphokinase values reached 29,200 (negative cardiac fraction) and peak serum theophylline level was 152 μg per ml.

The supraventricular tachycardia persisted through the second hospital day, then reverted to sinus tachycardia. Flaccid paralysis gave way to an awake, disoriented state. The patient was extubated on day 5. Oliguria and azotemia supervened; shunt placement and conventional hemodialysis were initiated on day 8. On day 12 she was readmitted to the intensive care unit and intubated because of a severe asthma attack with pulmonary aspiration.

Despite a stormy hospital course, the acute renal failure (felt secondary to the myolosis) resolved and the patient's usual mental state returned. She was discharged on the 45th hospital day weighing 75 kg (165 pounds).

Hypokalemia and elevated anion-gap metabolic acidosis have not been reported with theophylline toxicity and may, in the case described, be attributed to poor nutrition and acute circulatory collapse. Their presence should be sought in cases of suspected toxicity as they would be expected to contribute to the well-described occurrence of seizures and cardiac dysrhythmias.

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Patient Care Audits Not Cost Effective

TO THE EDITOR: Having just completed two years as Chairman of our hospital's Quality of Care Committee producing the required audits, I feel that little was accomplished in the way of improving patient care or in finding areas of needed medical education.

In reviewing the audits required during this time, I note that they did not uncover one single consistent defect in patient care either in methods or in the actions of specific physicians. As a matter of fact, the audits showed that either we provided good care or that our audits asked the wrong questions. The criteria selected must have been "governmentally" correct: the last ten audits reviewed by the San Francisco Peer Review Organization were rated as "very good"—5; "good"—2; "fair"—1, and "poor"—2. One "poor" audit on breast carcinoma received the low rating because of the "failure to take any action for criteria not met." Those criteria were documentation of pelvic and rectal examinations and vaginal smears. Our audit on cholecystectomy was graded as "poor" because "the criteria were not applicable to quality of care." Actually we took the areawide audit provided by the peer review organization in Sonoma County and used it. Evidently different peer review organizations have different viewpoints.

Having spoken with members of this type of committee in other hospitals, I find they share similar feelings.

We estimate the personnel hours spent on an average audit at 34 hours per audit. This is in pronounced contrast to 375 man hours that the University of California, San Francisco, reported it spent on a particular audit. Using our conservative figures and $10 per hour, this comes to $340 per audit. As there are approximately 3 million admissions in the 543 community hospitals in California, this should necessitate some 3,000 audits per year or a $1,200,000 expenditure. Adding on the bureaucratic expense for the gang downtown to shuffle papers, there is well over a $1.5 million expense each year in California alone for an almost nonproductive activity.

Who is to blow the whistle to stop this waste? It should be our colleagues who are officers of the peer review organizations. The San Francisco Peer Review Organization does not have any criteria for cease and desist limits on this program, and I doubt if anyone else does either. Not only are definitions of goals to be achieved in any program desirable, but limits of action need definition also to discontinue a program when it fails or has filled its purpose. But after all, when one is emotionally involved in a program it becomes difficult to speak out although other observers have.[1-3] As for me, I will no longer give my time or be associated with this program.

THOMAS E. WYNN, MD
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Communicating by Touch

TOUCH IS THERAPEUTIC. We talk to patients by the way we touch them. If you touch them roughly, you are telling them that you are not very interested in them, not very thoughtful of them. If you touch them gently, you speak to them and you reassure them. So, you talk with more than words, you talk with the way that you touch during examination. I would evaluate a very high proportion of ophthalmologists and other physicians as being much too rough in their touch, and certainly almost all students are. So please consider how you touch a patient.

—WILLIAM H. HAVENER, MD, *Columbus, Ohio*

Extracted from *Audio-Digest Ophthalmology*, Vol. 17, No. 6, in the Audio-Digest Foundation's subscription series of tape-recorded programs. For subscription information: 1577 East Chevy Chase Drive, Glendale, CA 91206

Refer to: Shulman AG: Absence of venereal disease in the People's Republic of China (Medicine in Perspective). West J Med 130:469-471, May 1979

Absence of Venereal Disease in the People's Republic of China

ALEX. G. SHULMAN, MD, *Beverly Hills, California*

IN THE COURSE OF giving talks to American audiences about health care in the People's Republic of China, I am frequently asked how it was humanly possible to eliminate venereal disease among that country's huge population in the relatively short time of 20 years.[1,2] In a country that in 1949, at the end of the Chinese civil war, had a population of about 650 million and a high incidence of venereal disease, this would seem to be an impossible task. To the Chinese authorities faced with this dilemma it also seemed impossible.[2-6]

The usual approach to the problem of venereal disease is represented by the methods employed by health departments in modern American or European cities. This involves asking doctors to report known cases of venereal disease and then trying persuasively to have those persons afflicted come to clinics for treatment. That such a system leaves much to be desired can be attested to by the venereal disease problem in the United States: far from being controlled, it has in recent years been getting totally out of hand by ever increasing and alarming proportions.

From United States government figures the venereal disease problem for the year 1976 was summarized as follows: Reported cases of gonorrhea rose from 945,945 in 1975 to 1,011,014 in 1976, an increase of 6.9 percent. It is estimated that at least 2,700,000 cases occurred in 1976. Syphilis ranked third among reportable communicable diseases in the United States; there were an estimated 360,000 untreated cases of syphilis in all stages in 1976. The particular economic cost for the United States in 1976 for gonorrhea was $212,000,000, while the hospital maintenance costs for patients with syphilitic psychosis was $60,714,000 for the year.[11] A report to the Senate Committee on Human Resources in 1978 stated that venereal disease among our 21 million adolescents (15 to 19 years old) is estimated to total more than 2.5 million cases a year.[12]

If such a conventional approach toward eliminating venereal disease had been tried in China in 1949 and the subsequent years, it was speculated that it would have taken decades to get around to all the contacts, if ever. Furthermore, the embarrassment and the stigma of having a venereal disease would keep large numbers away from treatment, thus concealing their venereal disease out of fear that disclosure would result in social ostracism.[3]

Social and Economic Factors

Taxes and interest on loans, which could never hope to be paid because of their huge size, were part of prerevolutionary China. There was the inevitable cycle of floods, which would wipe out crops and render millions homeless; and drought, which would do the same, reducing large percentages of the peasantry to despair. Frequently they had no choice but to relinquish their daughters to the prostitution pool which was part of the scene of every major city of that period. This was not a rare event. It was, in fact, the accepted norm in the early days of the twentieth century.[3,4,6] This was best illustrated in Shanghai where at one time there were reported to be an estimated 50,000 registered prostitutes and approximately twice that number of unregistered prostitutes.[6]

Since civil war raged on and off for some 20 years before formation of the People's Republic in 1949 and since Japanese troops were garrisoned in much of China between 1937 and 1945; the usual indifference of armies to human welfare, and the actions of soldiers to satisfy their sexual

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desires contributed enormously to the problem. The incidence of syphilis among the Japanese and government armies was over 20 percent.[3] After the defeat of Japan in 1945, government troops controlled large areas between 1945 and 1949 and added greatly to the venereal disease problem. There are statistics which showed "that the incidence of syphilis in the rural areas and small towns was proportional to the size of the Japanese and government armies and to the duration of their stay."[3]

The national minorities areas that were the most oppressed—such as Inner Mongolia, Gantze, Hainan Island and Kwangsi—had the highest rates of venereal disease (10 percent). The cities and urban areas had rates of 5 percent and the lowest rates were in the countryside (1 percent to 3 percent).[3]

Medical services for the peasants were virtually nonexistent in the old China. Most doctors were in cities, leaving the countryside with almost no medical care, and the poor could not pay private practitioners even where they were available. Ma Hai-teh (George Hatem), an American-born dermatologist living in Peking, pointed out that an injection of neoarsphenamine (Neosalvarsan) in 1940 would have cost a national minority herdsman a cow or a horse and few could afford this.[3] These impossible social and economic factors contributed to the spread of the diseases throughout the country.

In China after 1949, in a vast reconstructed socioeconomic program, the life-style of the peasants was raised by wiping out the previously exorbitant taxes, land rents, debts and usury. Jobs became available to all.[1-6] With this one change the economic reason for prostitution was wiped out, leading to the elimination rather than control of prostitution.

Measures to Control Venereal Disease

One of the first steps taken was the closure of all houses of prostitution throughout the country. The former prostitutes were organized into groups, and received physical examinations and treatment if necessary. Many of the girls were then trained to become factory workers, technicians or nurses, and were provided with jobs. Women from the countryside were often sent back to their own villages.[1,3,6]

In 1950 the Ministry of Health began to organize teams to work out preventive measures for venereal diseases throughout the country. Large networks of health care workers were established to help eradicate the diseases. To help accomplish this, a questionnaire was designed with ten questions giving possible clues leading a person to suspect he or she might have syphilis. Persons with such symptoms as skin lesions, falling hair or genital sores were invited to have an examination and blood test. In actual practice, one case of venereal disease was found among about 20 persons examined—and thus the problem of locating patients became manageable.[1,9]

To encourage people to report their disease without a social stigma, it was emphasized that they were not at fault in having their diseases. They were assured that no shame need be attached to it and that cure would be certain and free.

Large groups of unskilled persons, many in their late teens, were given a seven-day course on the principles of diagnosis and treatment. After rigorous training and then testing, more than 80 percent of these trainees qualified for the jobs of tracking down people with venereal disease and actually became the prototype of the later "barefoot doctors." Many doctors argued that this was unethical and would result in an unacceptably high rate of incorrect diagnoses.

Arguing strongly for the plan to use large numbers of young trainees was a group of doctors from the Research Institute of Dermatology and Venereology. In the forefront of the latter group was Dr. George Hatem, referred to earlier in this paper. Dr. Hatem is an American physician, the son of an immigrant Lebanese steelworker, who came from Buffalo, New York, and has been in China since 1936 where he took the Chinese name of Ma Hai-teh. Having witnessed at first hand the tragic plight of the Chinese people, he has dedicated his professional life to the struggle to eradicate a whole range of epidemic diseases. His most notable success was in the elimination of venereal diseases, especially syphilis[13] (an accomplishment that in the western world might make him a Nobel laureate).

Dr. Hatem's own paper[3] explains in great detail the enormous problems encountered, the struggle within the medical profession to utilize paramedical workers instead of standard existing epidemiological techniques, the ultimate clinical trials and finally, the successful outcome.

Thus in Ningtu County in Kiangsi Province, a pilot project was set up in which 3,000 of these trainees spent two months going out into the

countryside discussing the ten-part questionnaire and registering people believed to have symptoms. Results soon began to pour in. Examinations and treatments were given by the short-term trainees under the guidance of more experienced health workers.

The Research Institute of Dermatology and Venereology scientifically evaluated this group by random sampling. Their results were that with the young paramedical examiners, 90.2 percent of persons with venereal disease had been discovered and that in 89.7 per cent of cases a correct diagnosis had been made by the trainees.[1-3,6]

Such incredible success by relatively unskilled observers led to utilizing the method on a nationwide level. This method plus an enormous publicity campaign employing pamphlets, handbooks, outlines for talks, lectures, posters and plays to be used on radio and all newspapers paid the dividend of ultimately eradicating venereal disease from the land. By setting up rigid criteria for cure and control, many areas in China were free of disease by 1957. The large scale mass campaigns were over by 1966 when much of the above data were reported. Follow-up control measures still went on although it could be said that venereal disease was no longer a public health problem in China.[1-3,6-8,10]

Discussion

There were, then, three basic phases of the China campaign running concurrently: totally outlawing prostitution, broadly disseminating venereal disease information, locating and treating the victims. It is interesting to speculate on the question of whether such health measures might be applied to the venereal disease problem in the United States.

A free society guards its rights to privacy and to individual choice of behavior so tenaciously that the common welfare may at times be sacrificed in the process of protecting those rights. The right to have a venereal disease, to spread it to others and to ignore its treatment is just such a misplaced application of the democratic process. Prostitution is also an accepted fact of American life and to attempt its total elimination is completely unrealistic. An alternative might be mandatory government control of venereal disease, not just among prostitutes, most of whom are not known, but among all the people. A concerted nationwide media campaign on venereal disease using television, radio and press is feasible and desirable. Premarital venereal disease testing, while more effective in an earlier era, now misses large numbers of heterosexuals and homosexuals living together as couples without a marriage license. As for the endorsement of youthful volunteers to aid in seeking out those with disease, such a program is feasible, as was proven in wartime, but could only succeed in the positive atmosphere of a strong and meaningful public relations campaign.

By the time I arrived in China in 1975 I was told that medical schools no longer taught about venereal disease because there were no longer any cases to demonstrate to the students. Furthermore, silver nitrate drops are no longer put in the eyes of the newborn to prevent gonorrheal conjunctivitis.

To point up the present situation more dramatically I shall quote from an article in the Los Angeles County Medical Association bulletin written by a past-president of the Beverly Hills Chapter of that organization. He had visited China one year previously.

> I really did not believe that they had conquered venereal disease, but one evening at dinner I asked a senior urologist if they were seeing the new type of drug resistant gonorrhea. He replied that he hadn't seen a case of venereal disease in many years. "Oh yes" he remembered that "last year I saw a case referred in from one of the foreign embassies."[14]

This convinced the eminent Beverly Hills doctor that venereal disease is indeed under control in China.

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Refer to: Child JS, Cabeen WR Jr, Roberts NK: Hypertrophic cardiomyopathy and septal myectomy (Clinical Notes in Diagnostic Cardiology). West J Med 130:472-475, May 1979

Hypertrophic Cardiomyopathy and Septal Myectomy

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HYPERTROPHIC CARDIOMYOPATHY (also known as idiopathic hypertrophic subaortic stenosis) is an uncommon genetically transmitted (non-sex linked, autosomal dominant) cardiomyopathy characterized by pronounced left ventricular hypertrophy, particularly of the interventricular septum. This disease covers a spectrum, with one end being characterized by systolic displacement of the anterior mitral leaflet into the left ventricular outflow tract into apposition with the ventricular septum, resulting in dynamic left ventricular outflow tract obstruction and mitral regurgitation. Anatomic characteristics include (1) asymmetrical septal hypertrophy and (2) histologic septal (sometimes free wall) myofibrillar disorganization.

This uncommon, but by no means rare, process is of import to general medical practitioners because it may be confused with aortic valvular stenosis or coronary artery disease because of symptoms of exertional dyspnea or angina pectoris or because of abnormalities shown on electrocardiograms. Echocardiography may assist in diagnosis by showing asymmetric septal hypertrophy and, in those patients with left ventricular outflow tract obstruction, systolic anterior motion of the mitral valve.[1-3] Awareness of the safety and ability of echocardiography in diagnosis of hypertrophic cardiomyopathy can assist physicians in decisions regarding more invasive procedures (cardiac catheterization) and in institution of appropriate therapy.

A case is presented that exemplifies many of the characteristics of hypertrophic cardiomyopathy.

Report of a Case

A 34-year-old white man was well until 1974 when exertional dyspnea and syncope during exercise developed. He sought cardiologic advice. An echocardiogram and a cardiac catheterization were reported to show idiopathic hypertrophic subaortic stenosis. Propranolol (Inderal) therapy resulted in significant improvement but was discontinued in 1975 because of possible adverse psychiatric effects. The exertional dyspnea increased, and a precordial "pressure" sensation began to occur during exertion, relieved by rest and administration of nitroglycerin. An electrocardiogram during pain showed ST segment depression. Therapy with propranolol (40 mg given orally four times a day) was again instituted but the patient's symptoms did not greatly decrease. He discontinued his work in a mechanical parts shop. Because of increasing angina (occurring once or twice a day) with minimal exertion, as well as a near-syncopal episode, he was referred to the University of California, Los Angeles, Hospital in 1976. Family history showed that the patient's father had died suddenly at the age of 42 and had had no history of cardiac difficulties. It also was noted that a 28-year-old sister of the patient has a heart murmur (cause unknown).

On physical examination, blood pressure was 120/70 mm of mercury, pulse rate was 70 beats per minute (regular), no abnormal jugular venous distention or waves were noted and there was a double peaked carotid impulse (with normal upstroke and volume). The left ventricular apical impulse was palpable in the fifth left intercostal space just beyond the midclavicular line and was single. The first (S_1) and second (S_2) sounds were normal, but there was an atrial filling gallop audible at the apex. A grade III/VI high pitched crescendo-decrescendo (ejection) systolic murmur was heard at the apex and along the left sternal border, which began just after S_1 and ended before S_2. The murmur did not change with

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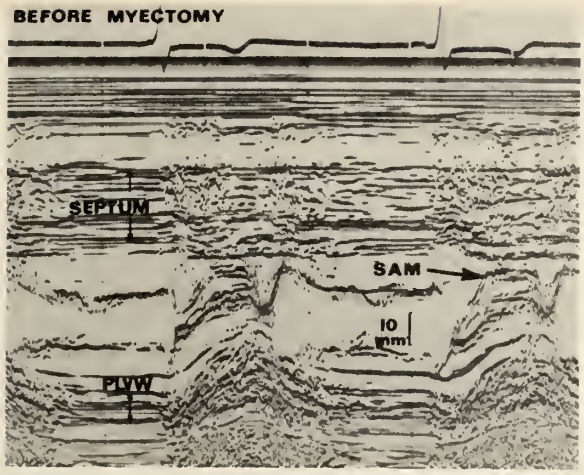

Figure 1.—Preoperative echocardiogram of mitral valve and left ventricle. Shown are the mitral valve with systolic anterior motion (SAM) and asymmetric septal hypertrophy (septum/posterior left ventricular wall [PLVW] ratio = 2.4). These findings are characteristic of hypertrophic cardiomyopathy with obstruction. Shown is a 10 mm calibration.

a Valsalva maneuver. No ejection click or diastolic murmur was detected.

A roentgenogram of the chest showed no abnormalities. An electrocardiogram showed left ventricular hypertrophy (voltage) and nonspecific ST-T abnormalities (strain). A standard M-mode echocardiogram gave the following findings: (1) asymmetric septal hypertrophy with a septal diastolic thickness of 24 mm and a posterior left ventricular wall diastolic thickness of 10 mm, with a resultant intraventricular septum/left ventricular wall ratio of 2.4; measurements were taken where the ultrasonic beam traversed the mid-left ventricle, at the tip of the anterior mitral leaflet, and at the mid-portion of the posterior mitral leaflet (Figure 1); (2) systolic anterior motion of the mitral valve consistent with left ventricular outflow tract obstruction (Figure 1); (3) a hypokinetic ventricular septum with normal posterior left ventricular wall motion and systolic thickening; (4) normal-to-small left ventricular diastolic dimension of 36 mm, taken at the peak of the R-wave, at a beam angle just below the tip of the mitral valve (not shown in the figure); (5) normal end-systolic size of the left atrium (36 mm) and of the aortic root (26 mm), and (6) midsystolic notching of the aortic valve (Figure 2), consistent with dynamic left ventricular outflow tract obstruction and reflecting the physical and phonocardiographic finding of a bifid carotid impulse.

Cardiac catheterization (rest, supine) showed a resting peak-to-peak gradient of 60 to 70 mm of mercury across the left ventricular outflow tract which notably increased in the postpremature ventricular contraction beat in association with a slight decrease in aortic pulse pressure.

Despite increases in propranolol dosage over six weeks to 400 mg per day, the symptoms and echocardiographic findings were unchanged. Consequently, a septal myotomy-myectomy was carried out. Postoperatively, there was a left bundle branch block. A postmyectomy echocardiogram showed a decrease in systolic anterior motion of the mitral valve, and a decrease in septal diastolic thickness to 17 mm (Figure 3).

Although there has been some decrease in symptoms in the patient, continued propranolol therapy has been necessary to provide adequate control.

Discussion

Hypertrophic cardiomyopathy may have no demonstrable left ventricular outflow tract ob-

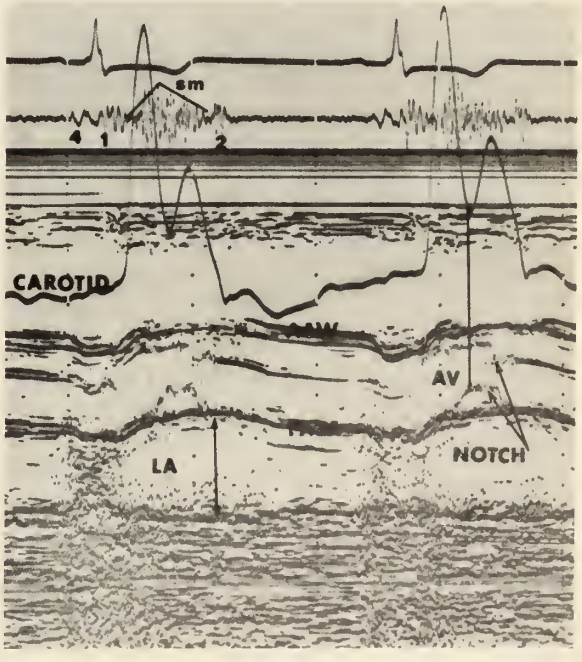

Figure 2.—Preoperative echocardiogram of aortic valve. Note the systolic notch of the aortic valve (AV) consistent with dynamic left ventricular outflow tract obstruction. This nicely correlates with the bifid carotid pulse tracing. The left atrium (LA) is normal in size. The phonocardiogram trace (from left lower sternal border) at the top of the figure shows the first (S_1) and second (S_2) heart sounds, an atrial filling gallop (S_4) and a crescendo-decrescendo murmur (outlined with solid lines). AAW = anterior aortic wall. PAW = posterior aortic wall.

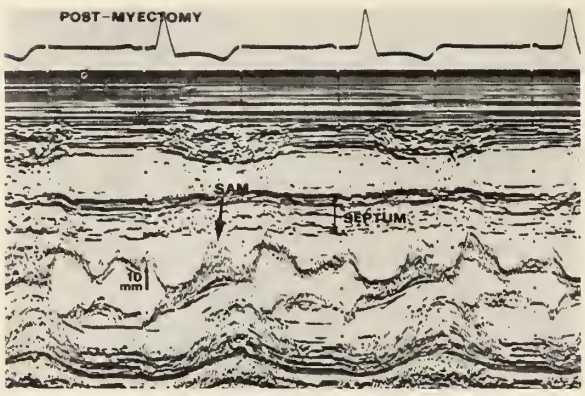

Figure 3.—Postmyectomy echocardiogram of left ventricle and mitral valve. The septum (17 mm) is now 7 mm thinner than the preoperative measurement (24 mm). Systolic anterior motion (SAM) is smaller in amplitude and duration than preoperatively, suggesting a lesser degree of outflow tract obstruction. The electrocardiographic lead now reveals an intraventricular conduction defect. Shown is a 10 mm calibration.

struction, or may have basal or provocable obstruction. Obstruction is due to systolic "tethering" of the anterior mitral leaflet into the left ventricular outflow tract and into apposition to the hypertrophied ventricular septum. The anterior mitral leaflet and upper ventricular septum in such patients show fibrous contact plaques pathologically. On physical examination, evidence for obstruction in the bifid carotid pulse, often a triple apex impulse, and a murmur are shown. Mitral regurgitation occurs in obstructive cardiomyopathy because of the abnormal systolic mitral valve motion. Such an abnormality renders these patients susceptible to bacterial endocarditis.

It is important to understand that the left ventricular outflow tract obstruction by the hypertrophied septum and mitral valve is a dynamic process governed by the following: (1) the force of left ventricular contraction; (2) the systolic left ventricular volume, and (3) the transmural distending pressure of the left ventricular outflow tract. Vasoactive drugs, such as digitalis glycosides or isoproterenol (increased inotropy) or nitroglycerin (decreased venous return), can increase obstruction and should be used with caution.

The postpremature ventricular contraction beat generates increased contractility and pressures in normal persons, in persons with fixed aortic stenosis and in persons with dynamic left ventricular outflow tract obstruction (hypertrophic cardiomyopathy). However, hypertrophic cardiomyopathy differs not in that the postpremature ventricular contraction gradient increases, but in that the postpremature ventricular contraction aortic pulse pressure is no greater than the prepremature ventricular contraction control.

Because exercise results in increased contractility, left ventricular outflow tract obstruction increases. Often as important is the immediate postexercise period when venous return decreases while sympathetic tone is still increased, therefore resulting in even higher gradients.

The Valsalva maneuver, or assuming the upright posture (squat to standing), decreases venous return, often causing an increase in obstruction, and on physical examination an increase in the intensity of the systolic murmur is noted. Similarly, hypovolemia may be poorly tolerated, as in surgical operations or parturition.

Just as important as left ventricular outflow tract obstruction is the restriction to left ventricular filling by decreased left ventricular compliance due, at least in part, to massive hypertrophy.[4,5] This results in an increase in left ventricular end-diastolic pressure and an increase in mean left atrial pressure. Physical examination, therefore, often shows an S_4 gallop. An increase in left atrial pressure and size predisposes to atrial fibrillation. This rhythm may be tolerated poorly by a stiff left ventricle because of the fast irregular ventricular rate and the decrease in available diastolic filling time. Also, the loss of the atrial "kick" may be important. Atrial fibrillation may be a medical emergency, and control of the heart rate is crucial, whether with propranolol or digoxin. Because systemic embolism is frequent, anticoagulation is necessary in the presence of atrial fibrillation.

Exertional dyspnea, as in our patient, is probably due to the left ventricular inflow obstruction and resultant increases in pulmonary venous pressure. The explanation for chest pain is less clear. The pain is often classic for angina pectoris, but the extramural coronary arteries are usually normal. Syncope and presyncope are often unrelated to the presence or absence of left ventricular outflow tract obstruction. Ventricular arrhythmias are accountable in some instances.

Sudden death is a major problem and is undoubtedly due in many instances to tachycardia or bradycardia. Worsened left ventricular outflow obstruction may also be contributory.

Because the symptoms described also may result from other diseases, echocardiography may be useful; if it gives the findings noted in the case discussed, a diagnosis of typical hypertrophic

cardiomyopathy with obstruction can be made (Figures 1 and 2). The dominant finding for hypertrophic cardiomyopathy (with or without obstruction) is asymmetric septal hypertrophy with a minimum septal/posterior left ventricular wall ratio of 1.3.[1] Integral to this criterion is that the septum is in fact thick (that is, thicker than 12 mm). Use of a higher septal/posterior left ventricular wall ratio (1.5 or more) is often recommended, and is preferred in our laboratory.[2] The septum is usually hypokinetic; that is, it usually has reduced systolic thickening and excursion.[3] In patients with left ventricular outflow tract obstruction, systolic anterior motion of the anterior mitral leaflet is also present, and usually midsystolic notching of the aortic valve.[3] The mitral valve typically touches the septum in diastole and often has a reduced diastolic closure rate. The left ventricular dimensions are almost always small-to-normal, and are essentially never increased. In addition, left atrial enlargement, with its propensity for atrial fibrillation, may be detected.

Treatment first should be directed at the significant risk of sudden death. Therefore, strenuous activity should be advised against to avoid inducing or increasing left ventricular outflow tract obstruction. Use of digitalis glycosides, nitroglycerin, isoproterenol or vigorous diuresis (or other causes of hypovolemia) may increase left ventricular outflow tract obstruction. Infective endocarditis prophylaxis should be recommended.

Propranolol (a beta-blocker) usually decreases left ventricular outflow tract obstruction due to tachycardia and sympathetic stimulation (such as exercise). It may also be useful in control of ventricular and atrial arrhythmias.

In the presence of pronounced basal left ventricular outflow tract obstruction, and disabling angina or syncope uncontrolled by propranolol therapy, with no alternative explanation for these symptoms, surgical operation may be indicated.[6] In the case discussed, septal myotomy-myectomy was carried out and there was some relief of symptoms. Of interest is the postoperative echocardiogram in this case (Figure 3) showing a thinner ventricular septum, and a decrease in systolic anterior motion of the mitral valve (suggesting a decrease in outflow obstruction). The only complication in the patient was left bundle branch block, a common finding. Other potential complications include ventricular septal defect and increased mitral regurgitation. Operative mortality in experienced hands is 5 percent.[7]

Prognosis appears to be worse with increased age, lack of obstruction, a high left ventricular end-diastolic pressure and, possibly, atrial fibrillation.[6] In general, those patients who are asymptomatic do well; those with symptoms have progressive difficulty. Surgical therapy seems to result in significant improvement in a large number of selected patients.[7]

Surgical therapy does not, however, have any clear-cut effect on the incidence of sudden death. Unfortunately, there are no clear clinical indicators that would help predict sudden death; one would expect, however, that detection by standard electrocardiography or Holter monitoring of significant arrhythmias may indicate a subgroup of patients at risk.

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Special Article

Refer to: Spensley J, Werme PH: Conservatorship: An involuntary legal status for 'gravely disabled' mentally disordered persons. West J Med 130:476-484, May 1979

Conservatorship: An Involuntary Legal Status for 'Gravely Disabled' Mentally Disordered Persons

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Since 1969 in California, conservatorship has been the only form of civil, long-term involuntary psychiatric legal process. It does not require hospital-based treatment.

This paper reports a preliminary study of this process through a retrospective analysis of conservatorship records in Sacramento County, California, from 1969 through 1976.

There is a steady overall increase in the incidence of conservatorships each year. A dramatic decrease in state hospital admissions preceded this increase. Referrals were predominantly (69 percent) from the private sector.

Once the first legal step was taken 87 percent of the patients completed the process and were placed on full conservatorship. Median age was 50; 52 percent were male and 90 percent were white. The relative proportion of single persons was high (45 percent). Diagnoses of schizophrenia and organic brain syndrome accounted for 86 percent of conservatees. About half (52 percent) terminate conservatorship after one year. No data were found which could be related to the character of treatment of conservatees. Future research in this area is urgently needed.

In California, conservatorship is the only form of civil, long-term, involuntary psychiatric legal process. Unlike provisions of previous commitment laws, it is a process that does not *require* hospital-based treatment. It is a legal process defined by statute under the California Welfare and Institutions Code based upon the concept of "grave disability."

Legislation inaugurating this process was implemented in 1969 with the following intent:

(a) to end the inappropriate, indefinite and involuntary commitment of mentally disordered persons and persons impaired by chronic alcoholism, and to eliminate legal disabilities; (b) to provide prompt evaluation and treatment of persons with serious mental disorders or impaired by chronic alcoholism; (c) to guarantee and protect public safety; (d) to safeguard individual rights through judicial review; (e) to provide individualized treatment, supervision, and placement services by a conservatorship program for gravely disabled persons; (f) to encourage the full use of all existing agencies, professional personnel and public funds to accomplish these objectives and to prevent duplication of services and unnecessary expenditures.

Conservatorship as a legal status may be granted only to persons who, through judicial process,

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have been determined to be mentally disordered or chronically alcoholic, or both, and who are "gravely disabled"—a condition characterized by inability to provide for the basic necessities of food, clothes and shelter.

Conservatorship action begins when a psychiatrist communicates to the office of the Public Conservator that he had found a person to be "gravely disabled." A Conservatorship Investigation Officer evaluates this report and if sufficient evidence exists, he or she prepares a report to the court indicating that the person is "gravely disabled" due to mental disorder or chronic alcoholism. The person for whom conservatorship status is sought has the right to request either a court or jury trial. Full conservatorship status is granted only after a formal court hearing, but the court may establish a temporary conservatorship on the recommendation of the officer providing conservatorship investigation. In this case, the Public Conservator would be appointed to act as temporary conservator for 30 days, unless the matter is continued by the court.

Conservators may be public officials or private persons (usually a relative) appointed by a judge on recommendation to the court by the Conservatorship Investigation Officer. They are responsible to the court for the person, the person's estate, or both the person and the estate, whichever the court decides. Thus, conservators determine the arrangements for food, shelter and care, and manage the person's estate if the court requires. They are officially charged to give priority to arrangements which would allow the person to return to home, family or friends.

Research literature on conservatorship is extremely sparse, as is research on the more general topic of involuntary psychiatric treatment. (While the "involuntary" status of a psychiatric patient used to be virtually synonymous with admission to hospital, in Sacramento County less than 10 percent of conservatees are residents of a state hospital.) In a study which carefully examines one aspect of conservatorship, Wilbert and coworkers[1] described a method of determining "grave disability" involving occupational therapy-like tasks. The task categories included budgeting, menu-setting, shopping, cooking, clothing and determining job plans, transportation and leisure activities. Acceptance of treatment was also measured. This study indicated that 90 percent of persons with a diagnosis of organic brain syndrome and who were determined by a psychiatrist to be "gravely disabled" failed the tasks. Chronic schizophrenic persons (the majority of cases), however, were much less uniform and only 70 percent failed the tasks that persons in other diagnostic categories (10 percent of the sample) failed only 20 percent of the time. The authors conclude that the test might be useful for persons in diagnostic categories other than organic brain syndrome. Evidence in addition to a psychiatric opinion is clearly important in light of these findings to substantiate the appropriateness of a determination of "grave disability."

The purpose of the present study is to gather basic descriptive data on the actual process of conservatorship so that a foundation may be established for future research in this controversial area. The data include the incidence and prevalence of conservatorship action, as well as demographic, placement and diagnostic data on the Sacramento County conservatorship population as it has been constituted since the 1969 implementation of conservatorship.

Mental Health Services in Sacramento

During the study period there were four principal treatment systems: (1) state hospitals, (2) University of California, Davis, School of Medicine Mental Health Centers, which operated under contract with the Sacramento County Mental Health Department, (3) general hospital based mental health centers and (4) private practitioners. The latter two systems interweave at several levels and for the purposes of referral source data analysis they are combined in the present study under the category "private." The university program administers three (of five) mental health centers in Sacramento County and the only 24-hour crisis service. Referrals from the general hospital mental health clinics are accepted by the university program when private hospital beds are full or their outpatient waiting lists are long. The University Mental Health Centers use a common hospital facility, the inpatient psychiatric unit of Sacramento Medical Center (27 beds at present).

Methodology

All 922 persons placed on conservatorship in Sacramento County from July 1969 through July 1976 were included in this study. Data were gathered from the records of the Public Conservator and from the Supreme Court. Initial referral data including diagnosis, age, race, sex, marital

status, referral source and initial placement were generally available from an up-to-date card file maintained by the Public Conservator's Office. This facilitated the coding of data for computer processing while at the same time ensuring strict confidentiality of individual records. The total sample was adjusted to avoid duplication in those rare cases in which there were multiple separate incidences (as opposed to renewals) of conservatorship action (four cases).

Data for last placement while on conservatorship, number of renewals of conservatorship and year of termination were obtained with considerable difficulty in the case of private conservatees. Approximately 30 percent of the cases had private conservators, and the records were kept at the Superior Court. The data were not summarized in any form and could be obtained only through laborious record review. For public conservatees, these data were available from the card file referenced above.

General population data and vital statistics were secured from county sources. State hospital population data were obtained from the State Department of Health. All adjusted general population rates were based upon 1970 census data.

Results and Discussion

Incidence of Conservatorship Action in Sacramento County

The data presented in Figure 1 show an overall steady increase in the absolute number of persons placed on conservatorship status each year.

In 1969, the first year of the conservatorship program, only 12 persons were assigned to conservatorship status. This rises to a projected high of 286 persons in 1976. Although this was not studied directly, the authors speculate that the increase could be the result of interaction among the following three major factors: (1) increased awareness in the community of conservatorship as a mechanism for dealing with "gravely disabled" persons, (2) changing therapeutic philosophies within community mental health programs in the county and (3) an increase in therapeutic failures in both public and private programs relating to an inability to treat and adequately care for larger and larger numbers of very ill patients who had been discharged from state hospitals to community programs over the years.

Bentz and Edgerton[2] cited community concern over the risk factor created by the existence of psychiatric patients in the community. With these concerns in mind, the present authors were interested in comparing patterns of state hospital admissions and conservatorships with homicide and suicide rates in Sacramento County. The data, as presented in Figure 2, show that although there was a dramatic decrease in state hospital admissions and an accompanying increase in the number of conservatees—that is, more "gravely disabled" persons in the community—there was not a concomitant dramatic increase in either the homicide or suicide rates. It would appear that, at least with regard to the latter two variables, the presence of former state hospital patients and an

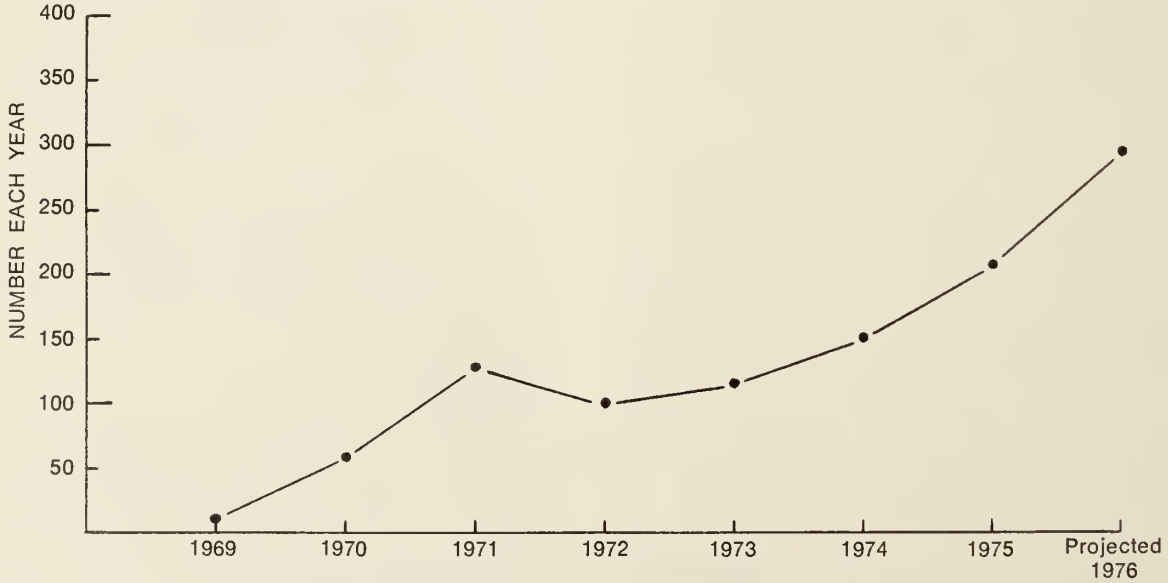

Figure 1.—Frequency distribution of year of assignment to conservatorship among all conservatees (N=922).

increasing number of conservatees in the community does not constitute a major community threat. This is in essential agreement with the findings of a prospective California study.[3]

Source of Referral to Conservatorship

Referral data were available on 920 (99.8 percent) of the 922 cases studied. There were three sources of referral to conservatorship action: (1) the University-based public mental health program, (2) the private sector and (3) state hospitals for the mentally disordered. Since state hospitals accounted for only 12 (1.3 percent) of the cases, this category was eliminated from subsequent analyses relating to referral source and comparisons were made between University-based and private referrals, leaving a data base of 908 (98.5 percent) of the 922 cases studied. Only six-

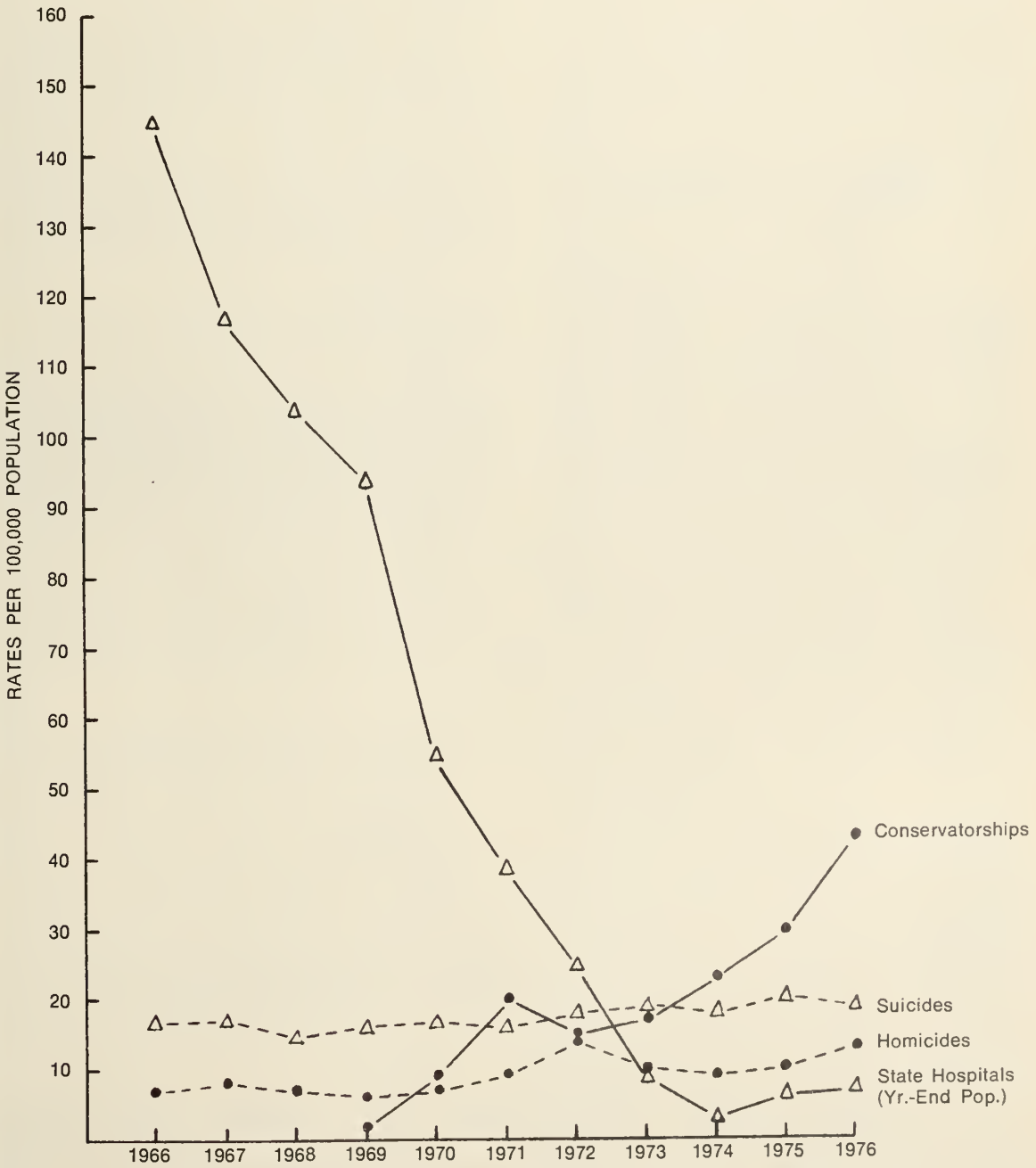

Figure 2.—Sacramento County rates per 100,000 population for state hospital residents, conservatorship actions, homicides and suicides; 1966-1976.

month data were available for 1976 due to the timing of the data collection and analysis.

Over the eight years of this study, 286 (30.7 percent) of the conservatees had been referred to conservatorship action by the university mental health program and 622 (69.3 percent) were referred from the private sector.

The data as presented in Table 1 and Figure 3 show the relative proportions of referrals per year.

The years 1969 through 1971 were characterized by a large influx of state hospital patients into the community following closure of programs at DeWitt and Stockton State Hospitals. Most of the patients who were referred to the university program were treated on a voluntary ambulatory basis through medication and aftercare clinic services. This was due primarily to the strong emphasis placed upon voluntary treatment by the university program at that time. As time progressed, it became possible to identify those patients among the large number of former state hospital patients for whom such voluntary ambulatory care was insufficient or inappropriate. These were then referred for conservatorship action.

In 1973 the shift in the curve was due primarily to the fact that the university program was required by the County Health Agency to evaluate all nursing home residents whose competence or willingness to remain as voluntary patients was questioned by the nursing home administrator. Before this time, patients were evaluated in nursing homes based upon uncooperative behavior or disruptiveness.

TABLE 1.—*Distribution of Major Sources of Referral to Conservatorship Action (N=908)*

	University Based		*Private*	
	N	*%*	*N*	*%*
1969	6	50.0	6	50.0
1970	34	57.6	25	42.4
1971	13	10.6	110	89.4
1972	24	24.0	76	76.0
1973	64	55.2	52	44.8
1974	53	35.1	98	64.9
1975	55	35.9	149	63.1
1976 ..... (6 months only)	37	34.9	106	65.1

Conservatorship Types: Public-Private, Temporary-Full

Public or private conservatorships are categories which distinguish between the types of conservators appointed for a given person. A public conservatorship occurs when a public official (the County Public Conservator-Public Guardian) is

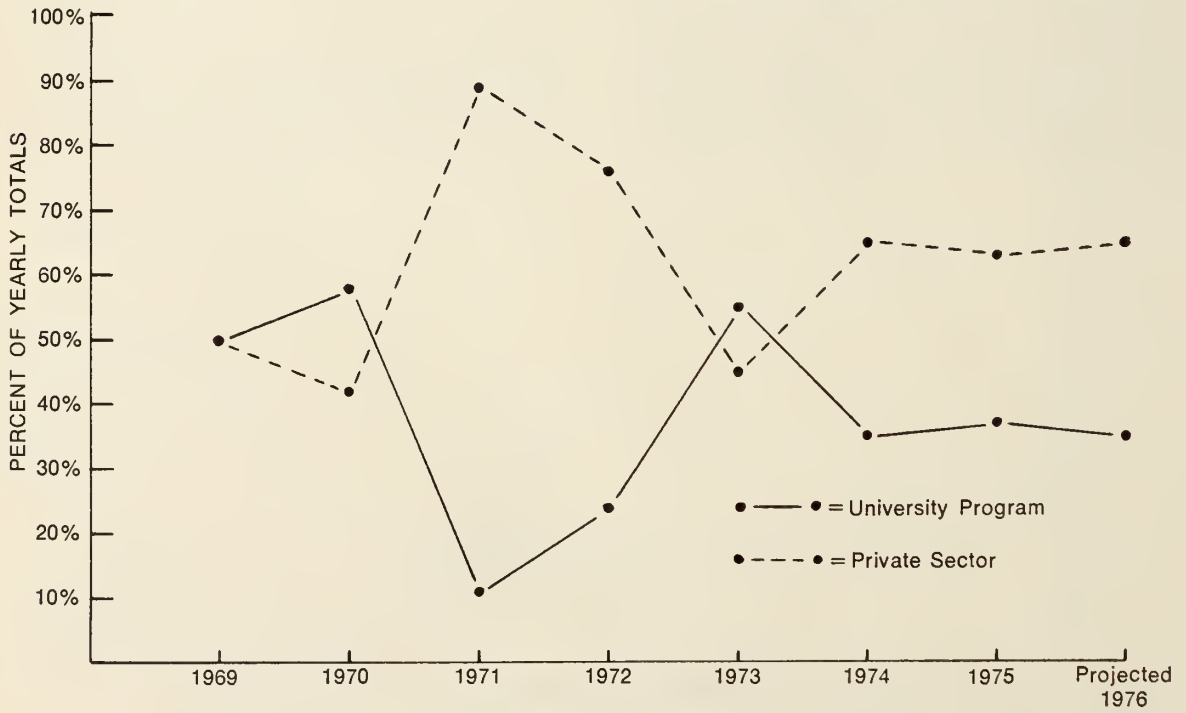

Figure 3.—Percent distributions of source of referral to conservatorship action among all conservatees by year of assignment to conservatorship.

TABLE 2.—*Percent Distribution of Age at Time of Assignment to Full Conservatorship Status (N=800)*

	19 Yrs. and Under	20-29 Yrs.	30-39 Yrs.	40-49 Yrs.	50-59 Yrs.	60-69 Yrs.	70-79 Yrs.	80 Yrs. and Over	Total
N	39	180	96	81	112	106	118	68	800
%	4.9	22.5	12.0	10.1	14.0	13.2	14.8	8.5	100.0

Range = 13-98 years. Median Age = 50 years.

appointed by the court as the conservator. A private conservatorship arises when the court appoints a private person (usually a family member) to act as conservator. In general, the Conservatorship Investigation Officer first attempts to interest a family member in serving as conservator, and only when no one is willing or able to serve does the court appoint the Public Conservator.

Among the 922 conservatorship cases studied, 69.7 percent of the conservatorship actions were public conservatorships, and in 30.3 percent of the cases a private conservator was appointed.

With regard to temporary versus full conservatorships, usually a temporary conservatorship is granted by the court before a decision relative to full conservatorship status. During this period, the Public Conservator's Office will gather data from the psychiatrist or treatment facility with regard to a person's mental health status. In addition, the person's financial status will be determined during this time. When all necessary information has been compiled, a court hearing is scheduled and a decision is reached as to whether or not the person is "gravely disabled" and should be placed on full conservatorship. Each person is represented by counsel of his choice at this hearing.

During the temporary conservatorship period, it sometimes becomes clear that the person is not "gravely disabled," and the Public Conservator may request that the court dismiss the petition. In other instances, a person might successfully challenge the conservatorship action before a judge or jury, with the result that full conservatorship is not imposed. In the present study, 118 (12.8 percent) of the 922 cases received *only* a temporary conservatorship. Cross tabular analysis with other data variables failed to show any significant relationships.

Demographic Characteristics of Conservatees: Age, Sex, Race, Marital Status

The percent distribution of age at the time of assignment to full conservatorship status is presented in Table 2. The age range was 13 through 98 years and the median age was 50 years. Persons aged 20 to 29 years accounted for the peak incidence (22.5 percent) while the next two decades have a relatively low incidence (12 percent and 10 percent, respectively). The low incidence of conservatorship in the middle age range causes one to wonder whether or not "grave disability" is defined differently according to age. An increased incidence in later decades would be expected due to the increasing frequency of severe organic brain syndrome with older ages. Future research might profitably examine this age variable more closely.

Data on sex showed that the relative proportion of males and females in the conservatorship population were virtually equal. Males accounted for 51.9 percent of the conservatees, and females accounted for 48.1 percent.

Racial or ethnic data were available for only 55.4 percent of the cases (511 of the 922 conservatees). The distribution of the 511 cases was as follows: 90.2 percent white, 6.3 percent black, 2.0 percent Spanish surname, 1.1 percent Asian and 0.4 percent American Indian.

Data on marital status showed that the relative proportion of single persons was strikingly high (45 percent), while married persons accounted for only 17 percent of the cases. It appears that the existence of a current marital partner militates against a person being placed on conservatorship.

Cross tabular analysis of marital status data by sex according to selected diagnostic categories showed a few interesting relationships. Among schizophrenic male conservatees 82.9 percent were single while 41.3 percent of schizophrenic female conservatees were single. Single schizophrenics appear to be more likely to be placed on conservatorship than those who are or have been married. The latter is particularly true for males. Conservatees with a diagnosis of organic brain syndrome are more likely to have been widowed, divorced or separated (53 percent). Among women with this diagnosis, 53.9 percent had been widowed (as compared with 13.5 percent for men). It may be that being widowed represents

TABLE 3.—*Percent Distribution of Marital Status Among All Conservatees (N=864)*

	Married	Single	Divorced	Separated	Widowed	Total
N	150	389	145	47	133	864
%	17.4	45.0	16.8	5.4	15.4	100.0

an extraordinary disruption and is a contributing factor to the "grave disability" of females with a diagnosis of organic brain syndrome.

Diagnostic Data

The diagnostic categories indicated in Table 4 are groupings of diagnostic codes based upon the *American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders* (DSM-II, 1968). "Affective Disorders" included all of the depressions as well as manic-depressive psychosis. "Other Psychosis" also included nonspecific diagnoses such as "Psychosis-Unknown Etiology" and "Paranoid States." It is clear from the distribution of diagnoses that those diagnostic categories representing the greatest degree of impairment are most heavily represented among the conservatees. The schizophrenia and organic brain syndrome categories account for 86 percent of the conservatees. This is what one would expect in a process whose definition is based upon a person being "gravely disabled."

Placement Data

"Last placement," as used in this study, refers to the place where the conservatee was located either at the time the data were collected or when the conservatorship terminated, whichever occurred first. Table 5 shows that nursing homes together with board and care homes accounted for 62.6 percent of all placements, while state hospitals accounted for only 9.7 percent. The largest proportion of conservatees (43 percent) had been placed in nursing homes. It will be important in future research to examine relationships between placement and such variables as diagnosis and public or private conservatorship status, as well as movement patterns between facilities and programs.

Renewals of Conservatorship

Conservatorship status for any given person is reviewed annually and, as a result of court action, is either renewed for an additional year or terminated. The data as presented in Table 6 indicate the number of renewals of full conservatorship according to the year that the persons

TABLE 4.—*Percent Distribution of Diagnostic Category Among All Conservatees (N=922)*

	Schizophrenia	Organic Brain Syndrome	Affective Disorders	Other Psychoses	Neuroses	Alcoholism	Other Personality Disorders	Total
N	507	286	32	81	4	41	21	922
%	55.0	31.0	3.5	3.4	0.4	4.4	2.3	100.0

TABLE 5.—*Percent Distribution of Last Recorded Placement at Time of Study Among All Conservatees (N=904)**

	Nursing Home	Board and Care Home	State Hospital	At Home	Jail	Other Placement	Absent Without Leave	Total
N	389	177	88	140	4	84	22	904
%	43.0	19.6	9.7	15.5	0.4	9.3	2.4	99.9

*Includes persons who died while on conservatorship or who had been discharged from conservatorship at the time of the study.

TABLE 6.—*Renewals of Conservatorship by Year of Original Conservatorship Action (N=482)*

	Number of Renewals of Conservatorship*													
	None		1		2		3		4		5		6	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
1969 (12)	9	75	0	0	0	0	1	8	0	0	1	8	1	8
1970 (56)	30	54	6	11	5	9	3	5	3	5	9	16	..	..
1971 (105)	41	30	15	12	13	11	16	13	23	19	..	..	..	..
1972 (93)	52	54	9	9	13	14	19	20	..	..	..	..	..	..
1973 (92)	53	46	8	7	38	33	..	..	..	..	..	..	..	..
1974 (124)	77	51	47	31	..	..	..	..	..	..	..	..	..	..

*Two dots (..) appear where there has been insufficient time for all possible renewals to occur.

were placed on conservatorship. The table is structured to reflect the fact that (at the time of data collection) there had been insufficient time for all possible renewals. Consequently, data are reported on 482 conservatees who were on full conservatorship and who had a chance to renew by the time of the study. It appears that on the average approximately 52 percent of all conservatees terminate conservatorship at the end of the first year. Based on the original conservatorship years 1970 through 1972 (where enough time has elapsed to analyze sufficiently), of those who renew conservatorship, approximately 10 percent of the original total number terminate each year thereafter. (We should point out that some of the terminations are due to the death of the conservatee, and the data have not been corrected to account for this. Only 9.5 percent of the total conservatorship population, however, had died while on conservatorship.) After the first year, only about 10 percent of the original number of conservatees renew *only* once. Therefore, if conservatorship status for a given person is not terminated at the end of the first year, there is a fairly high probability that conservatorship status will continue for at least two more years. Future research should definitely be devoted to identifying those variables which characterize the persons for whom conservatorship is renewed—that is, whose involuntary status is prolonged—compared with those persons who terminate conservatorship at the end of one year.

Treatment of the Conservatee

Essentially no data were found that could be related to the character of treatment received. Participation in programs such as outpatient psychotherapy, day treatment, vocational rehabilitation, activities programs and job training was not uniformly recorded in the records. Social functioning was not described at all and work status was rarely noted. Further, there is wide variability in the therapeutic programs of different nursing homes and board and care homes in Sacramento County.

A key assumption by authors who favor involuntary treatment is that involuntary treatment is beneficial to the persons so treated.[4-7] Unfortunately, only a few studies have examined the outcome associated with short-term involuntary treatment,[8-10] while extended involuntary treatment remains unstudied.

Polemical opinions dominate the psychiatric and legal literature with Szasz[11] and others, at one extreme, denying the appropriateness of involuntary treatment under any circumstances, and Treffert[12] and others, on the other extreme, saying that there is gross neglect of seriously disturbed patients which results in their "dying with their rights on."

Discussions

Data on conservatorship obtained through retrospective record review are inadequate to answer any of the fundamental questions about the propriety and effectiveness of involuntary treatment. Such data, however, do provide descriptions of both process and conservatee characteristics. These descriptive data become the source of a wide variety of interesting and important questions for future research.

Specific areas identified for more rigorous research are: (1) refinement and measurement of the concept of "grave disability," (2) comparison of conservatees with persons referred but not placed on conservatorship, (3) comparison of differential characteristics of "private" versus "public" referrals, (4) comparison of age groups with special attention paid to the possibility that "grave disability" is in practice defined differently according to age, (5) relationships between various characteristics of conservatees and their initial placement and, most important, (6) carefully designed treatment outcome studies.

Prospective research studies of the type suggested above require time, attention to ever present sources of bias and a major commitment of financial resources. The almost total lack of data on conservatees and the conservatorship process indicates how little attention has been paid to the important medical and legal questions surrounding this subject.

The medicolegal problem of the involuntary treatment of persons is of long standing and only successive approximations can be made toward its solution. Since institution of wide-ranging reform in mental health legislation was effected in California in July 1969 (Lanterman-Petris-Short Act and revision of 1957 Short-Doyle legislation), processes such as indeterminate judicial commitment have been stopped, new processes instituted and old institutions redefined. Conservatorship, or in essence the vesting of physical and financial responsibility for the gravely disabled conservatee by the court either in a publicly appointed con-

servator or a court-appointed volunteering private citizen for one year, subject to renewal by the court yearly, is one of these new institutions. Conservatorship changes involuntary treatment from an all-or-none phenomenon into a time-bound process, while also protecting the right of due process. These time limitations define and provide appropriate boundaries for rigorous scientific study.

A scientific appraisal of all involuntary treatment procedures is vital for the psychiatric profession. Much of the force of argument for a medical model for the determination of involuntary treatment rests with the implied benefits of treatment. Since the benefits of involuntary treatment remain controversial[11-13] and essentially unmeasured, scientific appraisal will not be an easy task. This, however, should not deter us from continued study of the process.

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Treatment of Legionnaire's Disease

THE ONLY WAY you can make the diagnosis is to suspect it and treat it empirically. The treatment of choice is probably erythromycin in a dose of 0.5 to 1 gram every six hours. That can be given intravenously, if necessary, or orally. The drug is rather irritating when given intravenously, so if the patient can take the medication orally, that's fine. The data that give us that information were from a challenge study in which guinea pigs were infected with the organism and then treated with various antibiotics. Erythromycin is by far the most effective . . . The same can be shown in tissue cultures and it can also be done on the agar plate much as the sensitivity testing is done in routine laboratory studies. However, the antibiotic susceptibility data generated that way indicate that the organism looks susceptible to many antibiotics. Clinically we know from the Legionnaire's outbreak, and related data, that many of those antibiotics are not effective in the therapy of this disease. So there still is some question about what other antibiotics would be appropriate. At present, erythromycin is the only really good choice; it is not clear what would be a second choice drug.

—PETER T. FRAME, MD, *Cincinnati*

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ARTICLES TO READ IN OTHER JOURNALS

EDITOR'S NOTE: *Members of the Editorial Board on occasion call attention to articles they consider to be important in other journals. These titles together with a brief assessment of the articles are published for the information of our readers.*

Perinatal Mortality and Morbidity in Breech Presentation

Descrespigny LJC, Pepperell RJ

Obstetrics and Gynecology
53:141-145, Feb 1979

DISCIPLINES: Obstetrics and Gynecology, Surgery, General Practice

READABILITY: Very good

In dealing with breech presentations these two obstetricians at the University of Melbourne are now delivering infants estimated to weigh 1,000 to 2,000 grams by cesarean section, once labor has begun. They reason that in doing this they will reduce the incidence of neonatal hyposia and intraventricular hemorrhage. Their neonatologists consider "salvageable" any infant weighing more than 1,000 grams.

—E. R. W. FOX, MD
Coeur d'Alene, ID

Prophylactic Cesarean Section Antibiotics: Maternal and Neonatal Morbidity Before or After Cord Clamping

Gordon HR, Phelps D, Blanchard K

Obstetrics and Gynecology
53:151-156, Feb 1979

DISCIPLINES: Obstetrics and Gynecology, Surgery, Pediatrics, General Practice

READABILITY: Very good

Pediatricians have voiced opposition to the prophylactic use of preoperative antibiotics in cesarean sections, fearing delayed infection in infants. Whether or not this is a valid objection (and it does not appear to be), these workers at the University of California, Los Angeles, Medical Center have shown that administration of antibiotics begun after the cord is clamped provides the same reduction in maternal morbidity as when initiated preoperatively.

—E. R. W. FOX, MD
Coeur d'Alene, ID

Transurethral Conversion of a Percutaneous Ureteral Stent to an Indwelling Stent

Bigongiari LR, Lee KR, Mebust WK, et al

American Journal of Roentgenology
131:1098-1099, Dec 1978

DISCIPLINES: Urology, Radiology, Oncology, Surgery

READABILITY: Good

An indwelling stent connects renal pelvis to bladder for palliative relief of ureteral obstruction. Surgical operation is avoided in debilitated or terminally ill patients.

—ROBERT B. ENGLE, MD
Orange, CA

Mammographic Parenchymal Patterns as Risk Indicators for Incident Cancer in a Screening Program: An Extended Analysis

Krook PM

American Journal of Roentgenology
131:1031-1035, Dec 1978

DISCIPLINES: Internal Medicine, Family Practice, Surgery, Oncology, Radiology, Gynecology

READABILITY: Good

Breast cancer is 7.6 times more likely to develop in women in the highest parenchymal risk pattern category than in those in the lowest category. Although the differences between categories are not as great, the paper provides further confirmation of Wolfe's work. Parenchymal patterns should aid in selection of high-risk patients for periodic mammographic screening.

—ROBERT B. ENGLE, MD
Orange, CA

Postoperaitve Bony Stenosis of the Lumbar Spinal Canal: Evaluations of 164 Symptomatic Patients with Axial Radiography

Quencer RM, Murtagh FR, Post MD, et al

American Journal of Roentgenology
131:1059-1064, Dec 1978

DISCIPLINES: Orthopedic Surgery, Neurosurgery, Neurology, Industrial Medicine, Radiology

READABILITY: Good

Computed tomography or transverse axial tomography is valuable in showing bony stenosis of the spinal canal. Plain films or myelography may fail to show alterations of shape of the spinal canal or focal bony overgrowth. These abnormalities are well shown by the axial studies. Of 23 patients treated surgically for narrowed spinal canal, 91 percent had clinical improvement.

—ROBERT B. ENGLE, MD
Orange, CA

Aspiration Biopsies of Chest Lesions

Lalli AF, McCormack LJ, Zelch M, et al

Radiology
127:35-40, Apr 1978

DISCIPLINES: General Medicine, Surgery

READABILITY: Very good

The fluoroscopy guided technique of biopsy under local anesthesia in 1,223 patients yielded a correct diagnosis in 86 percent, using an 18-gauge needle. Half of the patients were outpatients. The article is a good presentation of a useful, and often underrated diagnostic technique.

—H. JOACHIM BURHENNE, MD
Vancouver, BC

BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

CONTRARY TO NATURE—Cancer—Michael B. Shimkin, MD, Professor of Community Medicine and Oncology, University of California, San Diego, School of Medicine, La Jolla. DHEW Publication No (NIH) 76-720, US Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, 1977. 497 pages, $14.75; For sale by Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402; Stock number 017-042-00128-5.

Problems of current interest are often likely topics for historical investigation as well. It is surprising then that it has taken historians so long to deal with one of today's most complex medical problems: the origins, epidemiology and treatment of cancer. Three recent books deserve to be called to the attention of a wider readership. Richard Rettig's *Cancer Crusade* (Princeton University Press, 1977) was devoted to the political genesis and history of the National Cancer Act of 1971. He showed clearly why a "moon shot for cancer" was not a realistic venture. Very recently Professor L. J. Rather of Stanford has provided for us a superb study of the history of ideas of the understanding of cancer from antiquity through the 19th century in *The Genesis of Cancer* (Johns Hopkins Press, 1978). This is a thorough and scholarly account of ideas and of their acceptance and rejection in the best tradition of the history-of-ideas approach.

The third of the examples is Dr. Michael Shimkin's *Contrary to Nature—Cancer,* the book here reviewed. Shimkin, now of the University of California, San Diego, whose long career in cancer research eminently qualifies him to speak about our developing knowledge concerning cancer, has produced one of the most unusual books in the history of medicine that I have seen. It is not only unusual in its unique approach, but also in the immense amount of information it imparts while using relatively few words. This is an illustrated book in the very best sense. Cleverly mixing illustrations of concepts, important publications and people involved in the story, Dr. Shimkin has also provided a clearly written text that describes theories of cancer genesis, treatment, epidemiology and research institutes around the world. It could only have been written by someone with detailed knowledge of the field. Happily, Dr. Shimkin has brought to this his facility for explaining technical developments in easy to follow English prose.

In addition to descriptions of specific research developments, Dr. Shimkin has the instincts of the historian as well because he provides at numerous places in the text an explanation for trends in research. All this will be immensely valuable to any historian wishing to tackle the very difficult task of writing about the history of medicine in the 20th century. The numerous references that are so nicely provided for a reader interested in following the various paths of the story to their origins will also greatly enhance the usefulness of the book.

While Shimkin begins his history of our knowledge of cancer in ancient times and devotes far more space than is usually accorded to materials from before the 20th century, the prime focus, as is proper, is on recent decades. Anyone interested in the problems posed by cancer can benefit from seeing the story illuminated or being able to associate a face with a hitherto well-known but faceless name. Cancer is a problem for patients, but its scientific understanding is important for their proper care. Surely there is yet much to learn, but anyone foolish enough to decry the "war on cancer" as a medical Vietnam, should carefully read this book, not because it is a record of brilliant accomplishments but because it describes an exciting intellectual medical story.

GERT H. BRIEGER, MD, PhD
Professor and Chairman
Department of the History of Health Sciences
University of California, San Francisco

* * *

HANDBOOK OF TREATMENT OF MENTAL DISORDERS IN CHILDHOOD AND ADOLESCENCE—Editor: Benjamin B. Wolman, PhD, Professor of Clinical Psychology, Long Island University, and Editor-in-Chief, **International Encyclopedia of Psychiatry, Psychology, Psychoanalysis, and Neurology;** Co-Editors: James Egan, MD, and Alan O. Ross, PhD. Prentice-Hall, Inc., Englewood Cliffs, NJ (07632), 1978, 475 pages, $29.95.

This book is a collection of essays and reviews by authors from diverse theoretical backgrounds; some describe general methods of treatment while others apply these treatments to a wide variety of specific problems in childhood and adolescence.

The editors begin this task by boldly stating as a virtue what is, in their hands, a vice: "an artificial homogeneity in this highly diversified field was precisely what the editors avoided." In achieving this they have abandoned the readers altogether, leaving them to pick their way through the shoals of parochial theories and differing points of view without so much as an editorial lead line. For this reason the presentation falls between chairs. On the one hand it is not thoroughgoing enough to be encyclopedic for those advanced students who can do without guidelines. On the other hand it is not balanced and explanatory enough to orient beginning students. Chapters stating contradictory theses stand side by side without editorial comment and clarification to bridge the one to the next. Thus the failure of the book is not due to the contents of the chapters, some of which are excellent, but to the absence of any perceivable editorial help.

The book is bound in imitation leather, is oversized and is so elegant one would expect to find it on a coffee table rather than in a professional library. These factors must have contributed to the almost $30 price where the apparent purpose of the book, to provide a contemporary reference source, would call for a less expensive format in line with its three- or four-year half-life.

The major editor, Benjamin Wolman, PhD, a distinguished contributor to child psychology as a writer and editor in the past, seems to have put this book together as pot-boiler. He does not include something of his own important work but offers instead a brief and scattered first chapter, "The Rationale of Child Therapy," in which he introduces complicated and idiosyncratic ideas with completely inadequate exegesis so that one arrives at the end of the chapter with a spinning head and little more than the awareness that Wolman finds occasion to mention his own name no less than eight times in six pages. The remainder of the chapters are written in a readable and emphatic style, mostly by younger, well-qualified experts. One (perhaps the only) editorial virtue seems to be that the contributors were urged to include exhaustive bibliographies. For this feature alone I believe the book worth purchasing for libraries. Among the remaining 23 chapters some deserve to be singled out for comment.

(Continued on Page 490)

The 87th Annual Meeting

of the

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June 20-23 [illegible]

AT IDAHO'S SUN VALLEY

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An outstanding scientific medical program and beautiful green Sun Valley—this is a combination treat that should tempt all physicians to attend our 87th Annual Meeting of the Idaho Medical Association. Twelve credit hours of Category 1 are available.

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H. Kent Staheli, MD
President, Idaho Medical Association

87th Annual Meeting
Idaho Medical Association
Sun Valley • June 20-23, 1979

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IDAHO MEDICAL ASSOCIATION
87th Annual Meeting

Wednesday, June 20, 1979

8:30 a.m.-5:00 p.m. House of Delegates

Thursday, June 21, 1979

8:15 a.m. Introduction
FREDERICK K. MUELLER, MD
Program Chairman

8:30 a.m. All About the Hyperactive Child
LENDON H. SMITH, MD
Pediatric Consultant & Author

9:15 a.m. The Pathophysiology of Sudden Death and Myocardial Infarction
ROBERT S. ELIOT, MD
Director, Cardiovascular Center
University of Nebraska Medical Center

10:30 a.m. Immunology—Primer for Busy Physicians
PHILIP THOREK, MD
Medical Director,
Thorek Hospital and Medical Center
Chicago, Illinois

11:30 a.m. Logical and Scientific Treatment of Hypochondriasis
LENDON H. SMITH, MD

1:30 p.m. Hydraulics of Hypertension
DONALD W. FROOM, MD
Clinical Teaching Preceptor in Nephrology
Emanuel Hospital & Good Samaritan Hospital
Portland, Oregon

The Early Management of the Multiple Trauma Patient (An Organized Approach)
TERRY P. CLEMMER, MD
Director, Shock & Trauma, I.C.U.
L.D.S. Hospital
Salt Lake City, Utah

Use of the Newest Antibiotics
DeVON C. HALE, MD
Infectious Disease & Clinical Microbiology
Riverview Hospital
Idaho Falls, Idaho

2:45 p.m. Current Concepts of Contraception
KENNETH A. BURRY, MD
Assistant Professor, Obstetrics and Gynecology
University of Oregon Health Sciences Center

Treatment of Acute Asthma
CHARLES H. SCOGGIN, MD
Assistant Professor of Medicine
Division of Pulmonary Sciences
University of Colorado Medical Center

Friday, June 22, 1979

8:30 a.m. Rehabilitation & Prevention (Is There a Life after Myocardial Infarction?)
ROBERT S. ELIOT, MD

9:30 a.m. If I Had an Ulcer
PHILIP THOREK, MD

10:45 a.m. The Use and Abuse of Digitalis (Current Concepts in Digitalis Therapy)
ROBERT S. ELIOT, MD

11:30 a.m. A Potpourri of Materia Medica
LENDON H. SMITH, MD

1:30 p.m. Hydraulics of Hypertension
DONALD W. FROOM, MD

Nutrition in the Critically Ill
TERRY P. CLEMMER, MD

Use of the Newest Antibiotics
DeVON C. HALE, MD

2:45 p.m. Management of Menopause
KENNETH A. BURRY, MD

High Altitude Sickness
CHARLES H. SCOGGIN, MD

Saturday, June 23, 1979

8:30 a.m.-1:30 p.m. Closing Session, House of Delegates

REGISTRATION FEE $125 FOR NON-IMA MEMBERS AND OUT-OF-STATE PHYSICIANS.

For information contact:

IDAHO MEDICAL ASSOCIATION
P.O. Box 2668
Boise, Idaho 83701
Telephone: (208) 344-7888

(Continued From Page 486)

In a terse article Magda Campbell and Arthur Small put the administration of drugs to children and adolescents in perspective by pointing out that while the use of drugs in adults is to decrease symptoms, in childhood and adolescence the purpose of treatment includes the enhancement of development. They note that although drugs are in wide use (mostly by physicians not trained in child psychiatry) the state of psychopharmacology in the treatment of children is unsatisfactory and ought to be thought of only as an adjunct in the total treatment program.

There were four chapters on behavior therapy and its uses, beginning with a trenchant essay by Anthony Graziano who points out, quite rightly, that the contemporary criticisms leveled at behavior therapy can, and also should, be applied equally to the more traditional psychodynamic approaches. George Rekers provides an interesting review of uncontrolled case reports in the very difficult field of child and adolescent sexual problems. Here, as with some other conditions I could name, resistance to ordinary psychotherapeutic techniques is maximal and parental cooperation is minimal. Rekers describes innovative behavioral techniques and includes 11 pages of bibliography. Again, despite the fact that a good part of this book was given over to the topic of behavioral therapy, no attempt was made by the editors to organize or synchronize these chapters into a comprehensible treatment of the topic.

There could hardly be more disparity between treatment attitudes than is shown in Chapter 21, "Childhood Psychosis: Psychotherapy" by Clarie Kestenbaum, a sensitive, dynamically-oriented eclectic approach to inpatient psychosis and Chapter 22, "Childhood Psychosis: Behavioral Treatment," by Lovaas, Young and Newsom, which is all method and mechanics.

In summary, the book is a good resource to have at your local child psychiatry library. For your own bookshelf, however, it would be best to apply your $30 toward the Noshpitz four-volume *Handbook of Child Psychiatry,* coming out next year.

AUBREY W. METCALF, MD
Associate Clinical Professor of Psychiatry
University of California, San Francisco
Supervising Child Psychiatrist
Child and Adolescent Service
Langley Porter Institute
San Francicso

* * *

PROGRESS IN GASTROENTEROLOGY—Volume III—Edited by George B. Jerzy Glass, MD, Dr hon c (Univ. Nancy), Professor of Medicine, New York Medical College; Consultant in Gastroenterology, Memorial Hospital for Cancer and Allied Diseases, New York City. Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Avenue, New York City (10003), 1977. 1,052 pages, $88.50.

It has been seven years since Dr. Jerzy Glass' last review of *Progress in Gastroenterology* and the expansions of modern gastroenterology in this period have been explosive. Dr. Jerzy Glass has chosen seven areas of maximum interest: (1) proliferation and growth of the gastrointestinal mucosa, (2) gastrointestinal hormones, (3) gastrointestinal physiology and pathophysiology, (4) nutrition and the gastrointestinal tract, (5) cancer of the gastrointestinal tract, (6) clinical gastroenterology, (7) gastrointestinal endoscopy. The subjects included are a personal selection of what is new and important in gastroenterology. They vary from "pure science" reviews such as "Antitrophic Action of Gastric Autoantibodies on Parietal and Peptic Cells" to "pure clinical" reviews such as "Colonoscopy: Guidelines and Technique for Diagnosis and Therapy." As mentioned, these are selective reviews and there has been no attempt for this book to be comprehensive in scope. In all there are 39 authoritative review articles by recognized experts in their areas. Of the articles, 40 percent are written by foreign authors and the book has a truly international flavor. Despite the number of foreign writers, the English is readable and direct throughout the book and I commend the editors. The quality of the individual articles is generally excellent but varies somewhat, as is true in any multiauthored volume. The basic science reviews are uniformly excellent and the clinical reviews uneven. Some, such as "Therapeutic Programs in the Management of Duodenal Ulcer" are rather superficial and contentious and deal largely with obsolete material (cimetidine is not considered). Some are exactly current with much useful information such as the section on therapeutic endoscopy of the upper gastrointestinal tract.

The book is handsomely bound and well illustrated; the bibliographies are extensive and generally current.

This is not a book that a practicing physician would attempt to read from beginning to end. Rather, its purpose appears to be a compilation of advances in diverse areas of gastroenterology so that authoritative reviews in these diverse areas are instantly at one's fingertips. Accordingly, I would recommend this volume in the highest terms for reference libraries or the shelves of academic gastroenterologists. I would not recommend its purchase to the practicing generalists, internists, surgeons and gastroenterologists.

HOWARD A. SHAPIRO, MD
Clinical Professor of Medicine
Director, Gastroenterology Diagnostic Center
University of California, San Francisco
San Francisco

* * *

RECENT ADVANCES IN CLINICAL IMMUNOLOGY—Edited by R. A. Thompson, MBE, MBBS, BSc, MRCP, MRCPath, Consultant Immunologist, Director, Regional Immunology Laboratory, East Birmingham Hospital; Senior Clinical Lecturer, Department of Experimental Pathology, University of Birmingham. Churchill Livingston—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1977. 299 pages, $25.00.

In recent years, expansion of knowledge of immune mechanisms in disease has resulted in a profusion of textbooks and monographs on experimental and clinical aspects of immunology. It is therefore not unreasonable to ask what unique contribution any new text makes in this field. In this first volume of the *Recent Advances in Clinical Immunology,* the editor, R. A. Thompson, has brought together a group of investigators to discuss some of the developments in areas of immunopathology "which have taken great strides forward in recent years." The book encompasses an introductory chapter by the editor, five chapters by authorities from the United States of America, four from Great Britain and two from Europe.

It is not clear to this reviewer for whom this book is intended but, based on the title, one can presume that the editor has in mind practicing physicians with interest in clinical immunology. If this is so, then he has failed in his objectives and his audience is going to be disappointed. The chapters are of uneven quality, many lacking in substance and depth. Some useful information can be gleaned from chapters on protein malnutrition, amyloidosis, aging, and T and B lymphocyte subpopulations. The chapters dealing with antilymphocyte globulin and treatment of allergic diseases are a disappointment. One even wonders at the inclusion in a text dealing with recent advances of a chapter on the antilymphocyte globulin in which there has been virtually no progress in the last five years. On the other hand, the editor has seen

fit to exclude a discussion of the recent explosive developments in the major histocompatibility locus, a topic which is delegated to two paragraphs in the introduction. Although the editor points out in the preface that many aspects of clinical immunology are excluded because of space and recent coverage elsewhere, this line of reasoning may equally be applied to other topics as well.

In a text on immunology, inclusion of line charts and photomicrographs often adds much to clarify any confusing parts of the text. In this book, the photographs are of extremely poor quality, and although a good number of charts are included, many are small and fail to stand out adequately from the general text.

In summary, it is the feeling of this reviewer that this book offers little that is unique, and the physician who wants to brought up to date in clinical immunology will do better to spend his $25.00 elsewhere.

RAMAN PATEL, MRCP, FACP
Associate Professor of Medicine
Martin Luther King, Jr, General Hospital
Los Angeles

* * *

CLINICAL ASPECTS OF AGING—A Comprehensive Text Prepared under the Direction of The American Geriatrics Society—Editor: William Reichel, MD. Chairman, Department of Family Practice, Franklin Square Hospital, Baltimore. The Wililams & Wilkins Co., 428 E. Preston St., Baltimore (21202), 1978. 528 pages, $35.00.

It would be ungenerous not to welcome any systematic attempt to teach geriatrics. This one, particularly in Dr. Reichel's introductory article, and in its discussion of the influence of decent treatment and of environment on older patients, sets itself humane standards, and many of the authors are general authorities in their fields of specialism. However, the result is uneven in the extreme and suffers from a lack of focus in specific geriatric expertise. The book is a collection of essays, some leaning heavily on the routine content of specialist textbooks, but containing little, apart from the general advance of medicine, which was not in Cowdry.

A "comprehensive text" it isn't. European research in specific areas is almost wholly overlooked—thus we have incontinence without the studies of Brocklehurst, bone disorders without the work of Nordin and of Exton Smith, and endocrinology without any reference to the recent American and Russian work on hypothalamic clock models. Hypothermia does not appear to be mentioned: the section on decubitus ulcers says nothing about prevention and omits the predictive correlation of of ulcer risk with low frequency of movements in sleep, together with most recent work on the subject.

Even the name of the American Clive McCay is misspelled in both text and references (suggesting that reference was not made to the references, but to an intermediate source). This is not to say that some of the individual articles (that on dermatology is a good example) are not well done, or that the whole book contains nothing of profit for the student or practitioner, but the division between nongeriatrician specialists has proved unrewarding, since nowhere is there a single practical account of the differential diagnosis or natural history of "senility" as a presentation. On the other hand the elementary messages—overmedication, the nonspecific presentation of specific disease, physical causes of psychiatric disorder in the old, and the general bases of therapy—are addressed, and some of the specialist clinical material bears repetition.

There is still a need, however, for an American textbook as definitive as that of Brocklehurst, in which the writers are geriatricians first and other specialists second. Dr. Reichel might well write a more cohesive book by himself, since he has the right approach to the clinical field. In the meantime, courses in geriatrics can use the book but will have to lean for more specific instruction on imports.

ALEX COMFORT, MB, BCh
Consultant
Brentwood Veterans Administration Hospital
Los Angeles

* * *

THE CASTRATED FAMILY—Harold M. Voth, MD. Senior Psychiatrist and Psychoanalyst, Menninger Foundation, Topeka, Kansas. Sheed Andrews and McMeel, Inc., Kansas City, KS (6700 Squibb Road, Shawnee Mission, KS 66202), 1977, 239 pages, $9.95.

Harold Voth, MD, has superbly integrated 30 years of clinical experience with our current theoretical knowledge of the human condition. This synthesis results in a practical and useful model of how human beings develop, break down and respond to treatment.

Beginning with a biological base, Dr. Voth describes normal childhood development with particular emphasis on those factors that influence children's sense of maleness and femaleness. He then defines the role of father and mother in the family with such clarity that readers can easily identify pathological parenting. Most will be struck with how many children are exposed to an emotionally unhealthy environment during their formative years. Dr. Voth goes on to describe those life stresses—such as marriage, parenthood and work—that activate faulty developmental patterns and lead to psychiatric symptoms. He then explains the process and successful outcome of treatment, and in a section helpful to nonpsychiatrists describes how to choose an experienced and skilled psychotherapist. Finally, he examines America's cultural evolution and warns against the acceptance of social changes that adversely affect the nuclear family.

Written with the conviction of extensive experience and without jargon, *The Castrated Family* is a valuable addition to the library of anyone interested either personally or professionally in the influence of the family on the individual person.

JAMES CLIFFORD GREEN, MD
Spokane, Washington

* * *

CLINICAL ANATOMY OF THE HEART—Robert Walmsley, MD, DSc, FRCPE, FRCS Ed, FRSE, Emeritus Professor of Anatomy, University of St. Andrews, Scotland; and Hamish Watson, TD, MD, FRCPE, FRCP, FAAC, Chairman, Section of Cardiology, Department of Medicine, Postgraduate Dean and Director of Postgraduate Medical Education, University of Dundee; Consultant Cardiologist, Tayside Area, Scotland. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 230 pages, $49.50.

This book attempts to correlate the anatomy of the heart and great vessels in their *in situ* relationship in the thoracic cavity. This is done by a series of illustrations of transverse, coronal and oblique sections of the thorax. Many of the cardiac cuts are correlated with corresponding radiographs. There is also an introductory chapter which reviews the embryology of the heart in the same context. As the authors state, this book stresses the importance of studying the heart and great vessels with special regard to their position in living bodies.

The book is well illustrated by the series of thoracic sections and corresponding x-ray photographs. The text and illustrations are of excellent quality and should be of interest to cardiologists, cardiac surgeons, radiologists, and those interested in echocardiography and body scanning techniques.

JOHN E. CONNOLLY, MD
Department of Surgery
University of California, Irvine, School of Medicine
Irvine, California

in memoriam

AKESSON, HARRY NILS, Oakland. Died April 5, 1979 in Oakland, aged 74. Graduate of the University of California Medical School, Berkeley-San Francisco, 1932. Licensed in California in 1932. Dr. Akesson was a member of the Alameda-Contra Costa Medical Association.

DRAGOO, SAMUEL V., Santa Rosa. Died September 8, 1978 of pneumonia, aged 84. Graduate of the University of Illinois College of Medicine, Chicago, 1928. Licensed in California in 1928. Dr. Dragoo was a retired member of the Sonoma County Medical Association.

EAVES, GEORGE, Laguna Hills. Died March 11, 1979 in Laguna Hills of emphysema, aged 69. Graduate of the University of Minnesota Medical School, Minneapolis, 1939. Licensed in California in 1943. Dr. Eaves was a member of the Los Angeles County Medical Association.

FORBIS, ROBERT, JR., San Diego. Died March 11, 1979 in San Diego, aged 49. Graduate of the Washington University School of Medicine, St. Louis, 1955. Licensed in California in 1956. Dr. Forbis was a member of the San Diego County Medical Society.

FULLER, JOHN D., Santa Cruz. Died March 22, 1979 in Santa Cruz, aged 72. Graduate of the State University of Iowa College of Medicine, Iowa City, 1929. Licensed in California in 1937. Dr. Fuller was a member of the Santa Cruz County Medical Society.

HARTMAN, MILTON M., San Francisco. Died March 16, 1979 in San Francisco, aged 70. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1934. Licensed in California in 1934. Dr. Hartman was a member of the San Francisco Medical Society.

HENDERSON, JUSTUS D., Yountville. Died March 28, 1979 in Napa of heart disease, aged 66. Graduate of the University of Louisville School of Medicine, 1943. Licensed in California in 1944. Dr. Henderson was an associate member of the Napa County Medical Society.

HENNEY, JAMES EDWARD, Redwood City. Died February 10, 1979 in Redwood City, aged 57. Graduate of the University of Virginia School of Medicine, Charlottesville, 1949. Licensed in California in 1953. Dr. Henney was a member of the San Mateo County Medical Society.

HOMBACH, LEO J., Santa Cruz. Died March 20, 1979 in Santa Cruz, aged 81. Graduate of the Creighton University School of Medicine, Omaha, 1923. Licensed in California in 1932. Dr. Hombach was a retired member of the Santa Cruz County Medical Society.

LUNDQUIST, DELL THEODORE, Palo Alto. Died March 17, 1979 in Palo Alto, aged 79. Graduate of the Stanford University School of Medicine, Palo Alto-San Francisco, 1927. Licensed in California in 1927. Dr. Lundquist was a retired member of the Santa Clara County Medical Society.

MCDONNELL, CURTIS HARDIN, Sacramento. Died March 6, 1979 in Sacramento, aged 72. Graduate of the University of Michigan Medical School, Ann Arbor, 1932. Licensed in California in 1937. Dr. McDonnell was a retired member of the Sacramento County Medical Society.

MERRILL, BRUCE R., Belvedere. Died December 14, 1978 in Belvedere of heart disease, aged 67. Graduate of Harvard Medical School, Boston, 1938. Licensed in California in 1939. Dr. Merrill was a member of the Marin Medical Society.

NOGLER, ROBERT ALLEN, Bonita. Died March 7, 1979 in Bonita, aged 54. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1952. Licensed in California in 1952. Dr. Nogler was a retired member of the San Diego County Medical Society.

PEARLMAN, JEROME T., Los Angeles. Died February 3, 1979, aged 45. Graduate of Northwestern University Medical School, Chicago, 1957. Licensed in California in 1958. Dr. Pearlman was a member of the Los Angeles County Medical Association.

RICHARDS, GENE E., Sacramento. Died March 14, 1979 in Carmichael, aged 45. Graduate of Indiana University School of Medicine, Bloomington-Indianapolis, 1964. Licensed in California in 1965. Dr. Richards was a member of the Sacramento County Medical Society.

SELZER, LUDWIG, Santa Cruz. Died March 10, 1979 in Santa Cruz, aged 67. Graduate of Medizinische Fakultät der Universität, Wien, 1936. Licensed in California in 1940. Dr. Selzer was a retired member of the Santa Cruz County Medical Society.

STEINBERG, PAUL, Los Angeles. Died September 17, 1978 of heart disease, aged 82. Graduate of Ludwig-Maximilians-Universität, Medizinische Fakultät, München, Bavaria, Germany, 1922. Licensed in California in 1937. Dr. Steinberg was a member of the Los Angeles County Medical Association.

THRELFALL, DONALD R., San Jose. Died March 5, 1979 in San Jose, aged 73. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1930. Licensed in California in 1930. Dr. Threlfall was a retired member of the Santa Clara County Medical Society.

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INDICATIONS: *Therapeutically,* (as an adjunct to systemic therapy when indicated), for topical infections, primary or secondary, due to susceptible organisms, as in: infected burns, skin grafts, surgical incisions, otitis externa; primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia); secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis); traumatic lesions, inflamed or suppurating as a result of bacterial infection. *Prophylactically,* the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: This product is contraindicated in those individuals who have shown hypersensitivity to any of its components. Do not use in the eyes or in the external ear canal if the eardrum is perforated.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

When using neomycin-containing products to control secondary infection in the chronic dermatoses, it should be borne in mind that the skin is more liable to become sensitized to many substances, including neomycin. The manifestation of sensitization to neomycin is usually a low grade reddening with swelling, dry scaling and itching; it may be manifest simply as failure to heal. During long-term use of neomycin-containing products, periodic examination for such signs is advisable and the patient should be told to discontinue the product if they are observed. These symptoms regress quickly on withdrawing the medication. Neomycin-containing applications should be avoided for that patient thereafter.

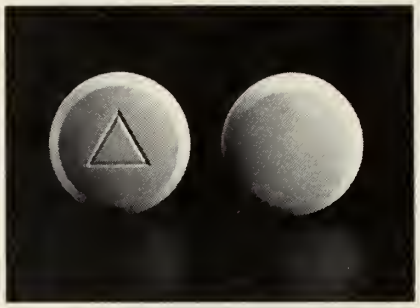
PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

The Maker

Examining a Few Myths About Prescribing.



Increasing pressure is being put on the practicing physician to prescribe drugs generically. You are told that brand-name products are universally "expensive" and generic versions are relatively "cheap." To make this case, the most extreme (rather than typical) price differentials are cited. Thus, consumers are led to believe that such differentials are commonplace. Even your knowledge and your motives as a physician are questioned.

Understandably, these views have created myths. We think it's time to examine them in the light of all the facts and ramifications.

MYTH: There are no differences in quality and performance between brand-name products and their generic counterparts. The corollary is that there are no differences among products made by high-technology, quality-conscious, research-based companies and those made by commodity-type suppliers.

FACT: The Food and Drug Administration does a good job in monitoring a generally excellent drug supply. Still, it has nowhere near the resources to guarantee the quality and bioavailability of all marketed products at any given time. Just a few months ago, for example, it noted that batches of tetracycline HCl capsules which met official monograph requirements were not bioequivalent to a reference product. As yo know, there is substanti literature on this subject affecting many drugs, in cluding such antibiotics as tetracycline and ery- thromycin. The record o drug recalls and court actions affirms strongly that there are difference among pharmaceutical companies and their products. Research- intensive companies have far better records than those that do no re- search and may practic minimum quality assur ance.

MYTH: Industry favors only "expensive" brand names and denigrates all generics.

FACT: PMA companies make 90 to 95 percent o the drug supply, includ- ing, therefore, most of t generics. Drug nomen- clature is not the impor tant point; it's the comp tence of the manufac- turer and the integrity o the product that count.

Matters.

MYTH: Generic options almost always exist.

FACT: About 55 percent of prescription drug expenditure is for single-source drugs. This means, of course, that for only 45 percent of such expenditure, is a generic prescribing option available.

MYTH: Generic prescriptions are filled with inexpensive generics, thus saving consumers large sums of money.

FACT: Market data show that you invariably prescribe—and pharmacists dispense—both brand and generically labeled products from known and trusted sources, in the best interest of patients. In most cases the patient receives a proven brand product. Savings from voluntary or mandated generic prescribing are grossly exaggerated.

MYTH: Drugs account for a major portion of the rise in health care costs.

FACT: Drugs represent a very small part of such costs. The amount of the health care dollar spent for prescription drugs was about 12 cents in 1967; today it is about 8 cents. And you as a physician are most conscious of how drug therapy can cut hospitalization, avert surgery, reduce office visits and keep patients on the job.

MYTH: Government intrusions into the marketplace will save tax money.

FACT: Government schemes always cost the taxpayer something, and the costs often exceed the benefits. Certainly, any federal "help," such as lists of wholesale drug prices sent to all physicians and pharmacists, will be no exception. Just think of the expense of keeping them current! Moreover, wholesale prices are poor guides to actual transaction prices and even worse guides to retail prices.

The PMA Position

We believe your freedom to prescribe, either by generic or brand name, should be totally unabridged. Otherwise, your prescribing prerogatives and your relationships with patients will be seriously impaired.

The maker does matter

After the myths about price and equivalency have been shattered, one fact stands out more clearly than ever: *The maker does matter.* As always, your best guide to drug therapy for your patients is to select products—both brands and generics—from manufacturers with credentials and performance records you have come to respect.

PMA

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Brief Summary of Prescribing Information

DESCRIPTION Each tablet of PERCOCET®-5 contains 5 mg oxycodone hydrochloride (WARNING: May be habit forming), 325 mg acetaminophen (APAP).

INDICATIONS For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS Hypersensitivity to oxycodone or acetaminophen.

WARNINGS Drug Dependence Oxycodone can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychic dependence, physical dependence and tolerance may develop upon repeated administration of PERCOCET®-5, and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, PERCOCET®-5 is subject to the Federal Controlled Substances Act.

Usage in ambulatory patients Oxycodone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. The patient using PERCOCET®-5 should be cautioned accordingly.

Interaction with other central nervous system depressants Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics or other CNS depressants (including alcohol) concomitantly with PERCOCET®-5 may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in pregnancy Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, PERCOCET®-5 should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in children PERCOCET®-5 should not be administered to children.

PRECAUTIONS Head injury and increased intracranial pressure The respiratory depressant effects of narcotics and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions or a pre-existing increase in intracranial pressure. Furthermore, narcotics produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute abdominal conditions The administration of PERCOCET®-5 or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Special risk patients PERCOCET®-5 should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, and prostatic hypertrophy or urethral stricture.

ADVERSE REACTIONS The most frequently observed adverse reactions include light-headedness, dizziness, sedation, nausea and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down.

Other adverse reactions include euphoria, dysphoria, constipation, skin rash and pruritus.

DOSAGE AND ADMINISTRATION Dosage should be adjusted according to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effect of narcotics. PERCOCET®-5 is given orally. The usual adult dose is one tablet every 6 hours as needed for pain.

DRUG INTERACTIONS The CNS depressant effects of PERCOCET®-5 may be additive with that of other CNS depressants. See WARNINGS.

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BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

THE ADOPTION TRIANGLE—The Effects of the Sealed Record on Adoptees, Birth Parents, and Adoptive Parents—Arthur D. Sorosky, MD; Annette Baran, MSW, and Reuben Pannor, MSW. Anchor Press/Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1978. 256 pages, $8.95.

ADVANCES IN HEART DISEASE—Volume 2—Edited by Dean T. Mason, MD, Professor of Medicine and Physiology; Chief, Cardiovascular Medicine, University of California, Davis, School of Medicine, and Sacramento Medical Center, Sacramento, CA—in the series CLINICAL CARDIOLOGY MONOGRAPHS—Series Consultants: J. Willis Hurst, MD, and Dean T. Mason, MD. Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Avenue, New York City (10003), 1978. 552 pages, $36.50.

AMERICAN MEDICINE: Challenges for the 1980s—David E. Rogers, MD, President, The Robert Wood Johnson Foundation; former Dean of the Medical Faculties and Vice President (Medicine), Johns Hopkins University; and former Professor of Medicine, Vanderbilt University. Ballinger Publishing Company, Harvard Square, Cambridge, MA (02138), 1978. 150 pages, $10.00.

ANNUAL REVIEW OF NEUROSCIENCE—Volume 2, 1979—Editor: W. Maxwell Cowan, Washington University School of Medicine, St. Louis; Associate Editors: Zach W. Hall, University of California, San Francisco; and Eric R. Kandel, College of Physicians and Surgeons of Columbia University, New York. Annual Reviews, Inc., 4139 El Camino Way, Palo Alto, CA (94306), 1979. 555 pages, $17.00 ($17.50 outside USA).

APPLIED THERAPEUTICS FOR CLINICAL PHARMACISTS—Second Edition—Edited by Mary Anne Koda-Kimble, PharmD, Associate Clinical Professor of Pharmacy, Vice-Chairwoman, Div. of Clinical Pharmacy, School of Pharmacy, University of California, San Francisco; Brian S. Katcher, PharmD, Lecturer in Pharmacy, School of Pharmacy, University of California, San Francisco; and Lloyd Y. Young, PharmD, Assistant Professor of Clinical Pharmacy, College of Pharmacy, Washington State University, Pullman. Applied Therapeutics, Inc., P.O. Box 31-747, San Francisco, CA (94131), 1978. 944 pages, $31.50, including shipping and handling charges.

AUTOBIOGRAPHY OF DYING—Archie J. Hanlan, PhD; Postscript by Mary S. Hanlan. Doubleday & Company, Inc., 245 Park Ave., New York City (10017), 1979. 193 pages, $8.95.

BETWEEN YOU AND ME: A Sensible and Authoritative Guide to the Care and Treatment of Your Skin—John A. Parrish, MD, Associate Professor of Dermatology, Harvard Medical School; Barbara A. Gilchrest, MD, staff dermatologist at Beth Israel Hospital, Professor of Dermatology, Harvard Medical School; and Thomas B. Fitzpatrick, PhD, Head of the Department of Dermatology, Harvard Medical School, and Chief of Service of the Dermatology Service, Massachusetts General Hospital, Boston. Little, Brown and Company, 34 Beacon St., Boston (02106), 1978. 239 pages, $8.95.

THE BRAND-NAME CARBO-CALORIE DIET—Donald S. Mart. Doubleday & Company, Inc., 245 Park Avenue, New York City (10017), 1973, 1979. 367 pages, $9.95.

CANCER IN CHINA—The Report of the American Cancer Delegation Visit to the People's Republic of China—Edited by Henry Kaplan, Director, Cancer Biology Research Laboratory, Stanford University Medical Center, Stanford, CA; and Patricia Jones Tsuchitani, Committee on Scholarly Communication With the People's Republic of China, National Academy of Sciences, Washington, DC. Alan R. Liss, Inc., 150 Fifth Avenue, New York City (10011), 1978. 240 pages, $28.00.

A CHANGE FOR HEART—Your Family and the Food You Eat—James M. Ferguson, MD, formerly Acting Director of the Eating Disorders Clinic, Stanford University Medical Center, and is now Medical Director, Gifford Mental Health Clinic, University of California, San Diego, School of Medicine; C. Barr Taylor, MD, Associate Director, Consultation Liaison Service for the Stanford Hospital; Director, Stress and Biofeedback Clinic at Stanford; and Phyllis Ullman, RD, Senior Research Dietician, Lipid Research Clinic, Stanford Heart Disease Prevention Program. Bull Publishing Co., P.O. Box 208, Palo Alto, CA (94302), 1978. 192 pages, $4.95 (Paperback).

CARDIAC ANESTHESIA—Edited by Joel A. Kaplan, MD, Associate Professor, Department of Anesthesiology, Director, Division of Cardiothoracic Anesthesia, Emory University School of Medicine, Atlanta, Georgia—in the series: CLINICAL CARDIOLOGY MONOGRAPHS—Series Consultants: J. Willis Hurst, MD, and Dean T. Mason, MD. Grune & Stratton, Inc., Medical and Scientific Publishers, 111 Fifth Avenue, New York City (10003), 1979. 530 pages, $44.75.

THE CARE OF THE DRUG DEPENDENT PREGNANT WOMAN AND HER INFANT—Enrique M. Ostrea, Jr., MD, Chief, Department of Pediatrics, Director, Newborn Nurseries, Hutzel Hospital, Associate Professor, Depart-

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ment of Pediatrics, Wayne State University School of Medicine, Detroit; With Cleofe J. Chavez, MD, Instructor, Department of Pediatrics, Research Associate, Department of Obstetrics and Gynecology, Joan C. Stryker, MD, Associate Professor, Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Administrator, Pregnant Addict Methadone Program, Hutzel Hospital. Michigan Department of Public Health, P.O. Box 30035, Lansing, MI (48909), 1978. 83 pages, $1.25 plus 75¢ postage and handling (paperback).

THE COURAGE TO FAIL—A Social View of Organ Transplants and Dialysis—Second Edition, Revised—Renée C. Fox, Professor, Departments of Sociology, Psychiatry and Medicine, and Annenberg Professor of the Social Sciences, University of Pennsylvania; and Judith P. Swazey, Professor, Socio-Medical Sciences Department, Boston University School of Medicine, and in Department of History, Boston University, and member of Special Scientific Staff (Pediatrics) at Boston City Hospital. The University of Chicago Press, 5801 S. Ellis Ave., Chicago (60637), 1978. 437 pages, $6.95 (Paperback).

CRITICAL CARE MEDICINE MANUAL—Edited by Max Harry Weil, MD, PhD, Chairman and Clinical Professor, Division of Critical Care Medicine and Director of the Institute of Critical Care Medicine, University of Southern California Schools of Medicine and Engineering, Los Angeles; and Protasio L. DaLuz, MD, Hospital das Clinicas da Faculdade de Medicine da Univ. de Sao Paulo, Brazil. Springer-Verlag New York Inc., 44 Hartz Way, Secaucus, NJ (07094), $22.50.

CURRENT MEDICAL DIAGNOSIS & TREATMENT 1979—Marcus A. Krupp, MD, Clinical Professor of Medicine Emeritus, Stanford University School of Medicine, Director of Research, Palo Alto Medical Research Foundation, Director of Laboratories, Palo Alto Medical Clinic; Milton J. Chatton, MD, Clinical Professor of Medicine, Stanford University School of Medicine, Senior Attending Physician, Santa Clara Valley Medical Center, San Jose, Research Associate, Palo Alto Medical Research Foundation; and Associate Authors. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1979. 1,130 pages, $18.00.

CURRENT TOPICS IN HEMATOLOGY—Volume 1—Editors: Sergio Piomelli, Division of Pediatric Hematology, New York University Medical Center, New York City; and Stanley Yachnin, Department of Medicine, University of Chicago. Alan R. Liss, Inc., 150 Fifth Avenue, New York City (10011), 1978. 235 pages, $24.00.

CURRENT NEUROLOGY—Volume 1—Edited by H. Richard Tyler, MD, Professor of Neurology, Harvard Medical School; Head, Section of Neurology, Peter Bent Brigham Hospital, Boston; and David M. Dawson, MD, Associate Profesor of Neurology, Harvard Medical School; Physician, Section of Neurology, Peter Bent Brigham Hospital. Houghton Mifflin Professional Publishers, Medical Division, Two Park St., Boston (02107), 1978. 499 pages, $29.00 (US), $37.50 (elsewhere).

CUTTING'S HANDBOOK OF PHARMOCOLOGY—The Actions and Uses of Drugs—Sixth Edition—T. Z. Csaky, MD, Professor of Pharmacology and Toxicology, University of Kentucky College of Medicine, Lexington; Adjunct Professor of Pharmacology and Toxicology, University of Louisville School of Medicine. Appleton-Century-Crofts, 292 Madison Ave., New York City (10017), 1979. 697 pages, $14.95 (Soft cover).

FETAL AND NEWBORN CARDIOVASULAR PHYSIOLOGY—Volume 1: Developmental Aspects; Volume 2: Fetal and Newborn Circulation—Proceedings of a Symposium to honor Donald H. Barron held in conjunction with the fall meeting of the American Physiological Society, August 11-14, 1976, Bryn Mawr, Pennsylvania—Edited by Lawrence D. Longo, MD, Loma Linda University; and Daniel D. Reneau, PhD, Louisiana Tech University, Ruston. Garland Publishing, Inc., 545 Madison Ave., New York City (10022), 1978. Volume 1: 631 pages; Volume 2: 513 pages, each, $39.50.

HANDBOOK OF CANCER IMMUNOLOGY—Volume 5: Immunotherapy—Edited by Harold Waters, PhD, Smithsonian Science Information Exchange, Washington, DC (At present, a Health Science Administrator, Division of Research Grants, NIH). Garland STPM Press, Division of Garland Publishing, Inc., 545 Madison Ave., New York City (10022), 1978. 475 pages, $37.50 (Five-volume set: $165.00).

HEALTHWISE HANDBOOK—Toni M. Roberts, Kathleen McIntosh Tinker and Donald W. Kemper. Healthwise, Incorporated, 111 South 6th Street, Boise, ID (83702), 1976, 1978, 1979. 260 pages, $6.95 from Doubleday & Company, Inc., 245 Park Ave., New York City (10017).

HEALTH THROUGH NUTRITION—A Comprehensive Guide for Cancer Patients—Ernest H. Rosenbaum, MD, Associate Chief of Medicine, Mount Zion Hospital and Medical Center, San Francisco; Carol A. Stitt, RD, Clinical Dietician, Mount Zion Hospital and Medical Center; Harry Drasin, MD, oncologist in private practice in San Francisco; and Isadora R. Rosenbaum, Medical Assistant, San Francisco. Life, Mind & Body, 1515 Scott St., San Francisco (94115), 1978. 120 pages, $5.95 (Paperback).

AN INTRODUCTION TO MEDICAL EDITING—Cathleen E. Swee, Medical Editor, Letterman Army Medical Center, Presidio of San Francisco, Published by Cathleen E. Swee, 3246 Anza Street, San Francisco (94121), 1977. 51 pages, $4.95, plus tax (Paperback).

RECENT ADVANCES IN CLINICAL NEUROLOGY—Number Two—Edited by W. B. Matthews, DM, FRCP, Professor of Clinical Neurology, University of Oxford; and Gilbert H. Glaser, MD, MedScD, Professor of Neurology and Chairman, Department of Neurology, Yale University. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 199 pages, $24.00.

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This listing of continuing education programs in California and Hawaii is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Committee on Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103; or phone (415) 777-2000, ext. 146. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

May 31-June 4—**California Society of Anesthesiologists—Annual Scientific Meeting.** Disneyland Hotel, Anaheim. Thursday-Monday. Contact: CSA, 100 S. Ellsworth Ave., Suite 806, San Mateo 94401. (415) 348-1407.

June 22-24—**Practical Closed System Anesthesia.** PMC. Friday-Sunday.

August 4—**Obstetrical Anesthesia.** Mercy Hospital and Medical Center, San Diego. Saturday. Contact: Gilbert E. Kinyon, MD, Dir. of Anesthesia, Mercy Hospital & Medical Center, 4077 Fifth Ave., San Diego 92103. (714) 294-8037.

September 15-22—**Practical Management of Anesthetic Problems.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 31½ hrs. $325.

CANCER

May 19—**Problems, Therapies and Complications in Cancer—Genital, Urinary and Colo-Rectal.** San Francisco Regional Cancer Foundation at Fireman's Fund Building, San Francisco. Saturday. 4 hrs. Contact: Terry Sheehy, PhD, S.F. Regional Cancer Fnd., 14th and Lake, San Francisco 94118. (415) 221-2132.

June 18-22—**Head and Neck Oncology.** UCLA. Monday-Friday. 35 hrs. $400.

July 13-14—**Oncology Symposium.** Area Health Education Center, UCSF, at Del Monte Hyatt, Monterey. Friday-Saturday. Contact: Remi Barron, Area Health Education Ctr., P.O. Box 1611, Salinas 93902. (408) 757-3616.

August 1-5—**20th Annual Advanced Seminars in Dermatology (Current Topics in Cancer)—Malignant Melanoma and Lymphoma.** See Medicine, August 1-5.

September 20-22—**Bladder Cancer.** American Urological Assn. at Hilton Hotel, San Diego. Thursday-Saturday. 16 hrs. $200, members; $250, nonmembers. Contact: Mary Rohan, AUA Office of Education, P.O. Box 1129, Aspen, CO 81611. (303) 925-2012.

September 26—**Head and Neck Cancer Symposium.** Hospital of the Good Samaritan, Los Angeles. Wednesday. 7 hrs. Contact: Janie Sternal, CME Coordinator, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

EMERGENCY MEDICINE

May 19—**Emergency Radiology.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7½ hrs. $50.

May 21—**Hand Injuries.** General Hospital Ventura Co. and Assn. of Emergency Physicians for Ventura and Santa Barbara Counties at General Hospital, Ventura. Monday; 7:30 p.m. 1½ hrs. (CMA and ACEP). Contact: Robert Andelman, MD, Gen. Hosp., 3291 Loma Vista Rd., Ventura 93003. (805) 654-3401.

June 2—**Orange County Emergency Medicine Workshop Part II—Assessment and Management of Chest and Abdominal Trauma.** UCI at Sheraton, Anaheim. Saturday. 6 hrs.

June 6-10—**Seminar in the Sierra: Postgraduate Course in Emergency Medicine.** Doctor's Essential Services, Inc., and Providence Hosp., Oakland, at Stanford Sierra Lodge, Fallen Leaf Lake, Lake Tahoe. Wednesday-Sunday. 21 hrs. $195. Contact: D. Craig Dennis, MD, 897 MacArthur Blvd., San Leandro 94577. (415) 632-1504.

June 16—**Abdominal Injuries.** DREW at New Otani Hotel and Garden, Los Angeles. Saturday. 8 hrs. Contact: S. Balasubramaniam, MD, Acting Dir. of Emergency Services, DREW.

June 18-22—**Advanced Emergency Medicine.** STAN. Monday-Friday. 25 hrs. $290.

June 20-22—**Symposium on Emergency Room Radiology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Thursday. 16 hrs. $160.

June 25-29—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

August 13-17—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 43 hrs. $350.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

September 8—**Orange County Emergency Workshop Part III—Neurological Trauma.** UCI. Saturday. 5 hrs.

September 24-28—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday. 43 hrs. $350.

MEDICINE

May 19-20—**Kidney Disease—19th Annual Symposium.** Kidney Foundation of So. Calif. at South Coast Plaza Hotel, Costa Mesa. Saturday-Sunday. Contact: Kidney Foundation of So. Calif., 1281 Westwood Blvd., Suite 200, Los Angeles 90024. (213) 473-6559.

May 23—**Diabetes Symposium.** Hospital of the Good Samaritan at Bonaventure Hotel, Los Angeles. Wednesday. 7 hrs. Contact: Janie Sternal, CME Coordinator, 616 Witmer St., Los Angeles 90017. (213) 488-8123.

June 1-3—**Infectious Disease.** Area Health Education Ctr., UCSF, at Del Monte Hyatt, Monterey. Friday-Sunday. Contact: Remi Barron, Area Health Ed. Ctr., P.O. Box 1611, Salinas 93902. (408) 757-3616.

June 4-8—**Advances in Internal Medicine.** UCSF at Hyatt on Union Square, San Francisco. Monday-Friday.

June 6—**Common Cardiovascular Problems in Children: An Update for the Practitioner.** American Heart Assn., Greater Los Angeles Affiliate, and Los Angeles Pediatric Soc. at Hilton Hotel, Los Angeles. Wednesday. 7 hrs. $40, AHA or LAPS members; $50, nonmembers. Contact: Jana Rogers, AHA, Greater LA Affiliate, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

June 9-10—**Practical Cardiology for the Primary Care Physician—Ischemic and Valvular Heart Disease.** UCLA. Saturday-Sunday. 13 hrs. $150.

June 10-12—**American Diabetes Association—39th Annual Meeting.** Century Plaza Hotel, Los Angeles. Sunday-Tuesday. 19 hrs. $25 for nonmembers. Contact: Harry A. Hansen, Dir. of Admin. Ser., ADA, 600 Fifth Ave., NY, NY 10020.

June 11-15—**Advances in Internal Medicine.** UCSF. Monday-Friday. 34 hrs. $300.

June 13-16—**Echocardiography: Fundamentals and New Developments in Cardiac Ultrasound.** American College of Cardiology at Sheraton Harbor Island Hotel, San Diego. Wednesday-Saturday. Contact: Mary Anne McInerny, Extramural Prog. Dept., ACC, 9111 Old Georgetown Rd., Bethesda, MD 20014.

June 15-16—**Recent Advances in Pheresis.** PMC at St. Francis Hotel, San Francisco. Friday-Saturday. 12 hrs.

June 15-July 28—**Summer Gerontology Institute.** See Of Interest To All, June 15-July 28.

June 20-22—**Pediatric Gastroenterology.** See Pediatrics, June 20-22.

June 27-29—**Hepatobiliary Disease in Clinical Practice.** PMC at Holiday Inn on Union Square, San Francisco. Wednesday-Friday. 15 hrs. $180.

July 13-15—**Cardiac Symptoms, Arrhythmias and Holter Monitoring.** International Medical Education Corp. at Hyatt, Anaheim. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

July 19-20—**New Approaches to Immunosuppression.** PMC at Fairmont Hotel, San Francisco. Thursday-Friday. 12 hrs. $100.

July 23-24—**Microcirculatory Approach to Current Medical and Surgical Problems.** Microcirculatory Society and American Heart Assn., Greater Los Angeles Affiliate, at Hilton, San Diego. Monday-Tuesday. 14 hrs. $175, before April 1; $200, thereafter. Contact: Nomi Feldman, Conf. Coordinator, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

July 27-29—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Sunday. 15 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

July 27-30—**Medical Mycology-Dermatomycology—4th Annual Course.** Memorial Hospital Medical Center-UCI Center for Health Education at Sheraton-Newport, Newport Beach. Friday-Monday. 36 hrs. $300. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

July 30-August 3—**Endocrinology and Metabolism.** UCSF at Hyatt Regency, San Francisco. Monday-Friday.

August 1-5—**20th Annual Seminars in Dermatology (Current Topics in Cancer)—Malignant Melanoma and Lymphoma.** Memorial Hosp. Med. Ctr.-UCI Ctr. for Health Education at Sheraton-Newport, Newport Beach. 14 hrs. $175. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 4—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

September 9-14—**Non-Invasive Diagnostic Technique in Vascular Disease.** UCSD at Sheraton Harbor Island Hotel, San Diego. Sunday-Friday. 35 hrs. $300.

September 16-20—**Pacific Dermatologic Association—Annual Meeting.** Hyatt Regency, San Francisco. Sunday-Thursday. 15½ hrs. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno NV 89509. (702) 323-2461.

September 24-28—**An Advanced Course for Internists.** STAN at San Francisco. Monday-Friday.

September 24-28—**Vascular Medicine and Surgery.** STAN at Stanford Court, San Francisco. Monday-Friday. 25 hrs. $290.

September 28-30—**Coronary Disease, Exercise Testing and Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton on the Wharf, San Francisco. Friday-Sunday. 13 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

OBSTETRICS AND GYNECOLOGY

May 21-23—**Recent Advances in Obstetrics and Gynecology.** UCSD at Vacation Village, San Diego. Monday-Wednesday. 18 hrs. $250.

August 6-12—**Reproductive Endocrinology, Infertility and Contraception.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 24½ hrs. $300.

August 25-31—**Edward Tyler Symposium on the Practical Management of the Infertile Couple—3rd Annual.** Tyler Medical Clinic, Los Angeles, and Univ. of Hawaii School of Medicine at Maui Surf Hotel, Maui, Hawaii. One week. 16 hrs. $200. Contact: Jetset Tours, 2029 Century Park East, Suite 2130, Los Angeles 90067.

PEDIATRICS

May 26-28—**Practical Problems in Pediatrics.** American Academy of Pediatrics, No. Calif. Chapter 1, at Del Monte Hyatt, Monterey. Saturday-Monday. $100, members; $125, nonmembers. Contact: Karen Brown, 604 Fortress Isle, Alameda 94501. (415) 523-3760.

June 6—**Common Cardiovascular Problems in Children: An Update for the Practitioner.** See Medicine, June 6.

June 18-20—**Pediatric Gastroenterology.** UCSF at Golden Gateway Holiday Inn, San Francisco. 13 hrs. $225.

July 28—**The Child's Hip: A Program for the Primary Care Physician.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7 hrs.

August 4—**Pediatric Dermatology Seminar.** See Medicine, August 4.

PSYCHIATRY

May 19—**Community Treatment of Schizophrenia.** Mental Research Institute, Palo Alto. Saturday. $60. Contact: MRI, 555 Middlefield Rd., Palo Alto 94301.

May 29—**Continuing Education for Psychiatrists.** UCD at UCD Medical Center, Sacramento. Tuesday. 3 hrs. $25.

June 8-10—**Family Therapy—Approaches and Techniques.** Cedars-Sinai Med. Ctr., Thalians Community Mental Health Ctr., and So. Calif. Psychiatric Soc. at Beverly Hilton, Beverly Hills. Friday-Monday. 15½ hrs. Contact: Ellen G. Ruderman, LCSW, Thalians Community Memorial Health Ctr., 8730 Alden Dr., Los Angeles 90048. (213) 855-3403.

June 13—**Diagnosis and Office Management of Anxiety and Stress.** LLU. Wednesday. 4 hrs.

June 15-July 28—**Summer Gerontology Institute.** San Jose State University. 6 weekend workshops. Contact: Cont. Ed., SJSU, San Jose 95192. (408) 277-2182.

June 16-23—**Comparative Psychiatric Therapies: Dynamic, Behavioral, and Pharmacological Approaches.** USC at Royal Lahaina, Maui, Hawaii. One week. 26¾ hrs. $300.

July 21-22—**Medical Aspects of Psychiatric Practice.** UCLA. Saturday-Sunday. 9 hrs. $150.

September 15—**Psychopharmacology in Clinical Practice: A Practicum in Mind-Allergy Drugs.** UCLA. Saturday.

RADIOLOGY AND PATHOLOGY

May 19—**Emergency Radiology.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7½ hrs. $50.

May 19-20—**Pathology of the Endocrine System.** UCLA at Long Beach Convention Center. Saturday-Sunday.

June 1—**Practical Laboratory Mycobacteriology.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday. 6 hrs. $60. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

June 14-15—**Modern Gastrointestinal Radiologic Techniques for the Practicing Physician.** UCSF at Hyatt on Union Square, San Francisco. Thursday-Friday. 13 hrs. $200.

June 20-22—**Symposium on Emergency Room Radiology.** See Emergency Medicine, June 20-22.

July 28-August 4—**Medical Imaging.** American College of Medical Imaging at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

September 13-May 8—**L.A. Bone and Joint Clinico-Pathological-Radiological Correlation and Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. 2nd Thursday of each month. 3 hrs./session. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 80801. (213) 595-3811.

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SURGERY

May 26—**Retinal Surgery Workshop.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $200. Contact: Lu Hendricks, Jules Stein Eye Inst., 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

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May 31-June 1—**Neurosurgery—9th Annual Postgraduate Course.** UCSF at Hilton Hotel, San Francisco. Thursday-Friday.

June 3-15—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Antonio De La Cruz, MD, Course Dir., ERI, 256 S. Lake St., Los Angeles 90057.

June 6—**Trauma: What's New or What Should Be Used?** UCD at Peach Tree Country Club, Marysville. Wednesday. 6 hrs.

June 14-16—**Highlights of Ophthalmology.** PMC. Thursday-Saturday. 15 hrs.

June 16—**Abdominal Injuries.** See Emergency Medicine, June 16.

July 23-24—**Microcirculatory Approach to Current Medical and Surgical Problems.** See Medicine, July 23-24.

August 4-11—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 28 hrs. $325.

September 24-28—**Vascular Medicine and Surgery.** See Medicine, September 24-28.

OF INTEREST TO ALL PHYSICIANS

May 15-21—**Diving Medicine, Basic.** UCSF at VA Hospital, Fresno. One week.

May 18-19—**UCSF—Alumni Day Program.** Friday-Saturday.

May 19-20—**Basic Skills in Sexual Counseling.** UCLA. Saturday-Sunday.

May 20-25—**Fingers-to-the-Toes: An Orthopedic Approach for the Family Practitioner.** UCD at Stanford Sierra Camp, Fallen Leaf. Sunday-Friday. 42½ hrs. $280.

May 21-25—**Orthopedics for the Primary Care Physician.** Bone and Joint Disease Foundation at Islandia Hyatt, Mission Bay, San Diego. Monday-Friday. Contact: Pat Curl, 5919 Caminito Yucatan, San Diego 92108. (714) 294-5944.

May 25-26—**Tropical Disease in the U.S.—Current Views on Diagnosis, Treatment and Epidemiology.** UCSF. Friday-Saturday.

May 26—**Differences in the Approach to Diseases and Treatment of the Elderly.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. $40. Contact: Prog. Coord., Center for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

June 1-2—**Care of the Dying Patient.** PMC at Golden Gateway Holiday Inn, San Francisco. Friday-Saturday. 12 hrs. $130.

June 2-3—**Family Practice Symposium—7th Annual.** So. Calif. Permanente Medical Group at Marriott Hotel, Newport Beach. Saturday-Sunday. Contact: Shirley Gach, SCPMG, Education & Research Dept., 4747 Sunset Blvd., 4th Floor, Los Angeles 90027. (213) 667-4516.

June 2-3—**Realistic Treatment for the Management of the Obese Patient.** UCLA. Saturday-Sunday. 13 hrs. $145.

June 7-9—**Common Problems in Primary Care.** PMC at Stanford Court, San Francisco. Thursday-Saturday.

June 7-9—**Clinical Application of Hyperbaric Oxygen—4th Annual Course.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Thursday-Saturday. 24 hrs. $150. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

June 11-16—**Family Practice Refresher Course.** UCI at South Coast Plaza Hotel, Costa Mesa. One week. 46 hrs. $290.

June 11-16—**Family Practice Review Course—6th Annual.** UCLA and Santa Monica Hospital Medical Center at Biltmore Hotel, Los Angeles. Monday-Saturday. 40 hrs. $300. Contact: UCLA.

June 13—**Diagnosis and Office Management of Anxiety and Stress.** LLU. Wednesday. 4 hrs. $30.

June 23-30—**Manipulative Medicine.** USC at Sheraton-Waikiki, Hawaii. One week. $325.

July 19-21—**Tissue Fluid Pressure and Composition.** UCSD. Thursday-Saturday. 17 hrs. $190.

August 4-11—**Hypnosis and Imagery: Practical Applications.** Bay General Community Hosp., Chula Vista, at Hotel Intercontinental, Maui, Hawaii. One week. 15 hrs. $150. Contact: Errol R. Korn, MD, 480 4th Ave., Suite 409, Chula Vista 92010. (714) 420-8051.

August 11-22—**Postgraduate Refresher Course—22nd Annual.** USC at Honolulu and Maui or Kauai, Hawaii. Two weeks. 39 hrs. $325.

August 19-24—**Family Practice Refresher Course—7th Annual.** UCD at Del Monte Hyatt, Monterey. One week. 30 hrs. $225.

August 25-31—**Edward Tyler Symposium on the Practical Management of the Infertile Couple—3rd Annual.** See Obstetrics and Gynecology, August 25-31.

September 1-8—**Manipulation, Mobilization and Related Techniques in the Treatment of Musculo-Skeletal and Myofascial Pain Syndromes.** USC at Sheraton Waikiki Hotel, Hawaii. One week. 27½ hrs. $325.

September 9-13—**American Academy for Cerebral Palsy and Developmental Medicine—Annual Meeting.** St. Francis Hotel, San Francisco. Sunday-Thursday. 26 hrs. $95. Contact: Helen Bryan, Assoc. Exec. Dir., 1255 New Hampshire Ave. NW, #1030, Washington, DC 20036. (202) 659-8251.

September 14-15—**The Last Horizon: Practical Solutions to Improved Patient Care of Patients with Terminal Illness.** UCD at Hyatt Lake Tahoe. Friday-Saturday. 15 hrs.

September 15—**Psychopharmacology in Clinical Practice: A Practicum in Mind-Allergy Drugs.** See Psychiatry, September 15.

September 20—**California Venereal Disease Controllers' Clinical Session.** CMA Task Force on Venereal Disease, Calif. VD Controllers Assn. and Calif. Academy of Preventive Medicine at San Mateo. Thursday. Contact: Karin McGhee, CMA.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

OREGON

COUNCIL ON MEDICAL EDUCATION

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, 97213.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Audi-

torium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

INTERNAL MEDICINE

May 17-19—**Oregon Society of Internal Medicine/American College of Physicians Annual Meeting.** Jantzen Beach Red Lion, Portland. Contact: Joyce Gullixson, Oregon Society of Internal Medicine, 5210 SW Corbett Avenue, Portland 97201.

OF INTEREST TO ALL PHYSICIANS

Circuit Course Programs—Contact: Joyce Gullixson, Oregon Medical Association, 5210 SW Corbett Avenue, Portland 97201.

May 17 (Albany)—**Pediatrics.** Albany General Hospital, 1:30 p.m.

May 17 (Lincoln City)—**Urology.** North Lincoln Hospital, 1:30 p.m.

May 23 (Salem)—**To Be Announced.** Salem Hospital, 1:30 p.m.

May 23 (Grants Pass)—**Medical Genetics.** Josephine General Hospital, 1:30 p.m.

May 24 (Klamath Falls)—**Medical Genetics.** Presbyterian Intercommunity Hospital, 1:30 p.m.

May 30 (Astoria)—**Office Psychiatric Problems.** Columbia Memorial Hospital, 1:30 p.m.

May 30 (Ontario)—**Office Gynecology.** Holy Rosary Hospital, 1:30 p.m.

May 31 (Bend)—**Dizziness/Syncope and Loss of Consciousness.** St. Charles Hospital, 1:30 p.m.

June 4-6—**Update: Emergency Medicine.** Salishan Lodge, Gleneden Beach. Contact: Richard A. Tuscher, DO, 2900 SE Steele St., Portland 97202.

June 7—**Medicine Day 1979—Infectious Diseases.** Eugene, Valley River Inn. Contact: John D. Wilson, MD, Eugene Hospital and Clinic, 1162 Willamette Blvd., Eugene 97401.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.

May 19—**Upper Extremity Orthopedics in Primary Care.** Seattle, Saturday. Group Health Cooperative of Puget Sound. Contact: Office of Education, Group Health, A-5, 201 16th Avenue E., Seattle, WA 98112. (206) 326-7348.

May 19-20—**Extracapsular Cataract Surgery and Artificial Lens Implantation: The Northwest Course.** Bellevue, Saturday-Sunday. Overlake Hospital. Contact: David J. McIntyre, MD, Northwest Microsurgical Institute, Inc., 1035 116th Ave., NE, Bellevue, WA 98004. (206) 454-7912.

PACIFIC MEDICAL CENTER

Course Offerings April-July, 1979

APRIL 21
Diagnostic Imaging for Primary Care Physicians

MAY 3-5
Critical Care Cardiology

JUNE 1-2
Care of the Dying Patient

JUNE 7-9
Common Problems in Primary Care

JUNE 14-16
Highlights of Ophthalmology

JUNE 15-16
Recent Advances in Pheresis

JUNE 22-24
Practical Closed System Anesthesia

JUNE 27-29
Hepatobiliary Disease

JULY 19-20
New Approaches to Immunosuppression

JULY 26-28
Microcomputers in Office Practice

For information write:
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May 22—**Gynecologic Cancer—Univ. of Wash. OB-GYN Sessions** (Spokane). Tuesday, 12-1 p.m., Sacred Heart Medical Center, Spokane. Contact: Wm. Harvey Frazier, MD, West 101 8th Ave., Spokane, WA 99204. (509) 838-8347.

May 31 and June 1—**Respiratory Care.** Seattle, Thursday-Friday. Contact U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 1—**Management of Acute Surgical Problems.** Seattle, Friday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 1-2—**Northwest Association of Physical Medicine—Child and Adult Developmental Disabilities.** Bellevue, Friday-Saturday. Holiday Inn. Contact: Donald E. Silverman, MD, Providence Medical Center, 500 17th Ave., C-34008-1, Seattle, WA 98124. (206) 326-5701.

June 2-3—**Colon and Rectal Surgery.** Seattle, Saturday-Sunday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 7-8—**Surgery.** Seattle, Thursday-Friday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 21-23—**American College of Cardiology: Medical and Surgical Management of Coronary Artery Disease.** Seattle, Thursday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 23-24—**The American Medical Heritage: Hematic, Heroic and Heretical.** Sun Valley, Idaho, Saturday-Sunday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

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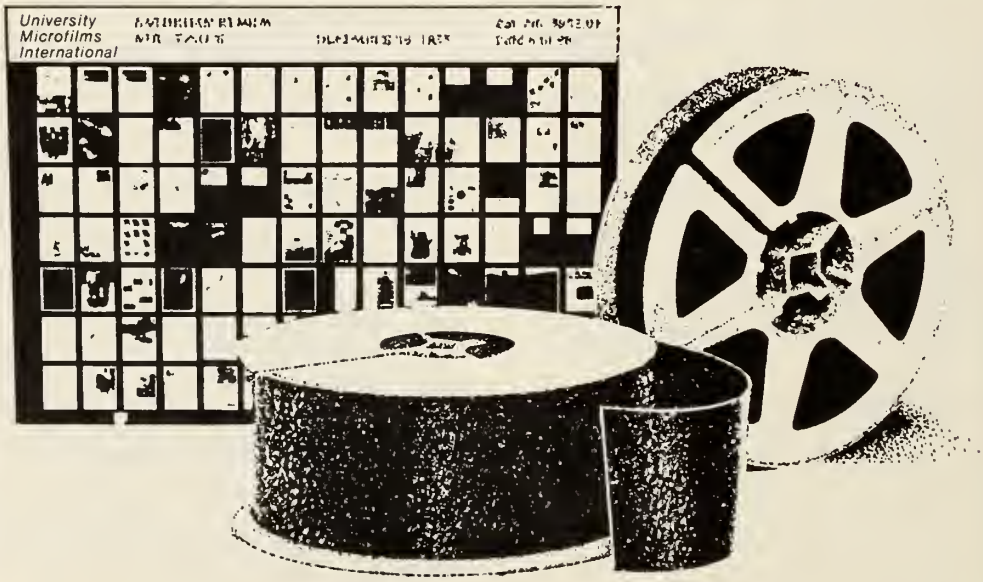

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June 25-26—**Platelets and Clotting—Univ. of Wash. Internal Medicine Review Sessions.**

June 25—Monday, Wenatchee. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, Wenatchee Valley Clinic, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

June 26, Tuesday, Yakima. 5-7 p.m., Memorial Hospital. Contact: Harry Kimball, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

August 16-18—**Controversies in Otolaryngology.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

ALASKA, MONTANA AND IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

June 6-8—**Alaska State Medical Association Annual Meeting**—Sitka, Wednesday-Friday. Shee Atika Lodge. Contact: Alaska State Medical Association, 1135 W. 8th Ave., Suite 6, Anchorage, AK 99501. (907) 277-6891.

June 27—**Diabetes in Pregnancy—Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

August 22—**Dysplasia and Early Cervical Neoplasia**—Univ. of Wash. OB-GYN Sessions (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

MONTANA

May 16-17—**Pediatric Psychiatry—Univ. of Wash. Pediatrics Sessions.**

May 16, Wednesday, Great Falls. Contact: Jerrold Eichner, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

May 17, Thursday, Kalispell. 11:30 a.m.-1 p.m., Kalispell Hospital. Contact: Ronald Miller, MD, 4th and Baker, Whitefish, MT 59937. (406) 862-2515.

May 19—**Sports Medicine for Primary Physicians**—Missoula, Saturday. Western Montana Clinic. 7 hrs. Contact: A. G. Peterson, MD, Western Montana Clinic, 501 W. Broadway, Missoula, MT 59801. (406) 549-6181.

June 1-2—**Billings Clinic Foundation Medical Surgical Symposium**—Billings, Friday-Saturday. Northern Hotel. Contact: Paul Grmoljez, MD, P.O. Box 2555, Billings, MT 59103. (406) 252-4141.

June 6-8—**Acute Respiratory Failure and Health Effects of Asbestos—Univ. of Wash. Internal Medicine Review Sessions.**

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WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: June 6-8, 1979, Shee Atika Lodge, Sitka.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 25-29, 1979, Safari Hotel, Scottsdale.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: February 7-13, 1980, Town and Country, San Diego.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 19-23, 1979, the Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 8-12, 1979, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: June 20-23, 1979, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 4-6, 1979, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: May 18-20, 1979, Ely Convention Center, Ely.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: May 2-4, 1979, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Meeting: November 2-4, 1979, OMA Headquarters.

Utah State Medical Association—42 S. 5th East St., Salt Lake City 84102. Annual Meeting: September 11-14, 1979, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 4-7, 1979, Washington Plaza Hotel, Seattle.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: August 28-31, 1979, Jackson Lake Lodge, Moran.

June 6, Wednesday, Great Falls. 4:30-7:30 p.m., Deaconess Hospital. Contact: F. John Allaire, MD, 1220 Central Ave., Great Falls, MT 59401. (406) 454-2171.

June 7, Thursday, Billings. 7-9:30 a.m., Marillac Hall. Contact: Mrs. Frances Burt, Marillac Hall, Billings, MT 59101. (406) 657-7083.

June 8, Friday, Missoula. 8:30-11 a.m., St. Patrick Hospital. Contact: Mrs. Janet Perrin, 525 West Pine, Missoula, MT 59801. (406) 549-3782.

June 21-23—**Montana Academy of Family Physicians' 29th Annual Scientific Assembly.** Fairmont Hot Springs. Thursday-Saturday. Contact: R. Bruce Beithon, MD, Twin Bridges, MT 59754. (406) 684-5642.

August 9-11—**Montana/Wyoming Chapter, American College of Surgeons' Annual Meeting**—Big Sky. Thursday-Saturday. Meadow Village. Contact: Charles F. Rinker, MD, 300 N. Willson, Bozeman, MT 59715. (406) 587-0704.

September 7-8—**Montana/Wyoming Chapter, American College of Physicians' Regional Meeting**—Fairmont Hot Springs, Friday-Saturday. Contact: J. E. McGreevey, MD, 401 S. Alabama, Butte, MT 59701. (406) 723-4384.

IDAHO

May 21—**Gynecologic Cancer—Univ. of Wash. OB-GYN Sessions** (Boise). Monday. 12-1 p.m., St. Luke's Hospital, Boise. Contact: David M. Barton, MD, 999 N. Curtis Rd., Boise, ID 83704. (208) 385-9391.

May 22—**Pediatric Pathology: Role of the Laboratory in Pediatric Diagnosis—Test Selection and Interpretation—Univ. of Wash. Pediatrics Sessions** (Pocatello). Tuesday. 12 noon, St. Anthony Hospital. Contact: William Hogan, MD, 527 E. 12th Ave., Pocatello, ID 83201. (208) 232-1443.

June 23-24—**The American Medical Heritage: Hematic, Heroic and Heretical**—Sun Valley. Saturday-Sunday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

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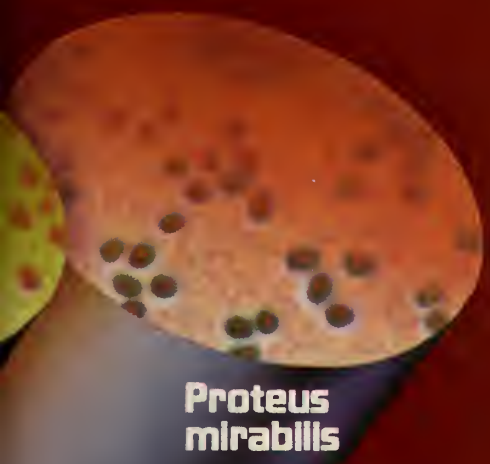

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Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

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The inexpensive, in-office culture tests for *Trichomonas vaginalis,* Candida (Monilia), *N. gonorrhoeae*

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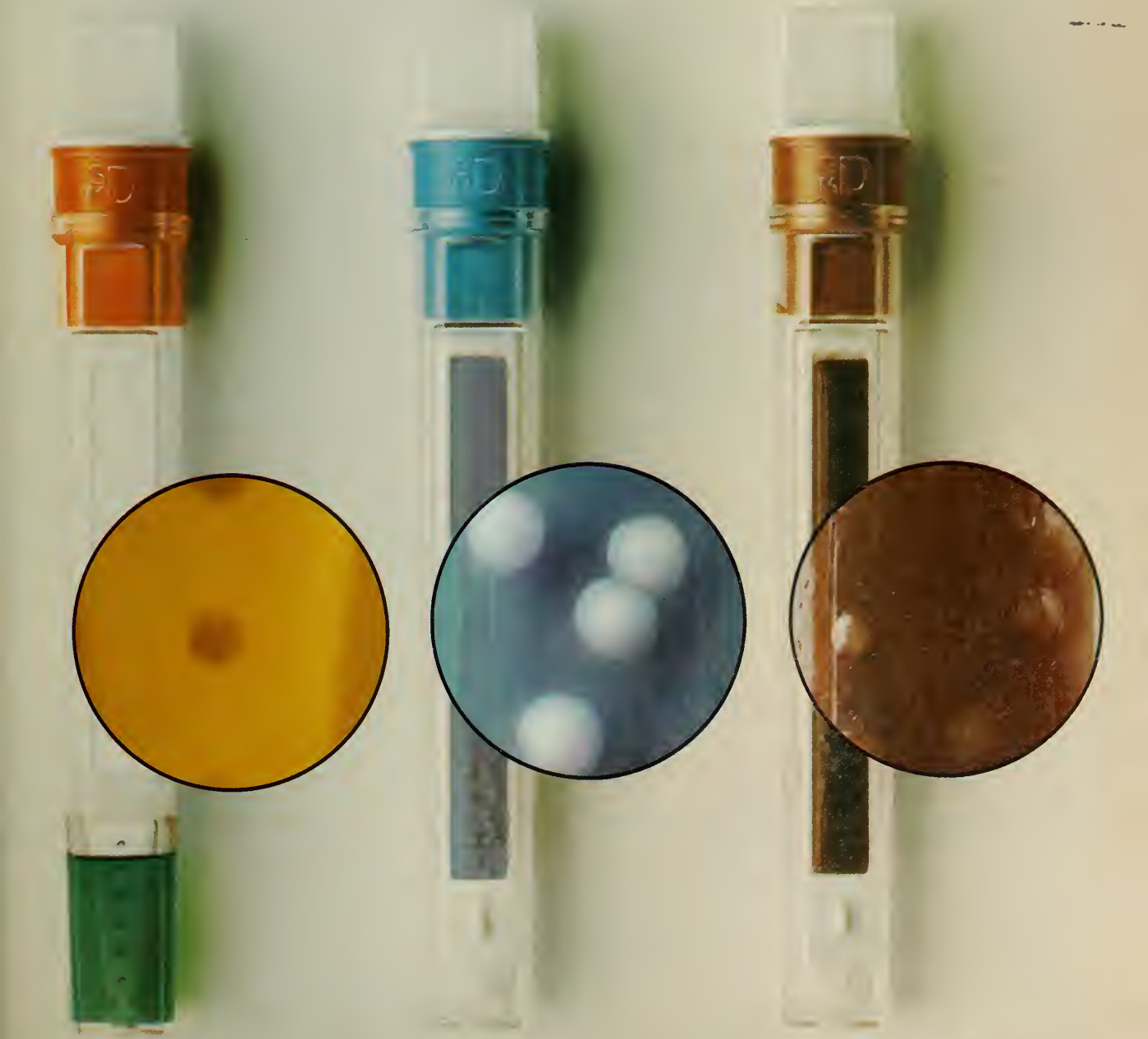


SmithKline Diagnostics

880 West Maude Avenue, P.O. Box 1947, Sunnyvale, CA 94086 • (408) 732-6000

SKD
a SmithKline company

Personally, Steve could never speak up for milk.

In TV commercials, you'll often see people speaking up for milk. Steve Allen and his wife Jayne Meadows are also seen on TV telling viewers about Mocha Mix... 100% milk free!

Matter of fact, this non-dairy creamer would have been found in their home way before they ever filmed the Mocha Mix series of commercials. Steve is allergic to milk products. Yet, he likes the splash of luxury and fresh taste in his coffee, on cereal, fruit and dessert, even in cooking. For the Allen household, Mocha Mix is the perfect answer.

It could well be the answer for many people who rely on you for their dietary needs, those with an allergy similar to Steve's, or a lactose intolerance. And, for many who must maintain a fat-restricted diet you should know that Mocha Mix is one non-dairy creamer that contains no coconut oil, giving it the highest ratio of unsaturated to saturated fat of any creamer. It easily exceeds the accepted standard 2:1 ratio. It's 100% cholesterol free, too. No wonder Mocha Mix is not just another non-dairy creamer, but the one you can rely on most for your patients who can't speak for milk, either.

NUTRITION INFORMATION

Portion Size 1 Fluid Ounce (2 Tbs.)	
Servings Per Container	16
Calories	40
Protein	0 grams
Carbohydrate	3 grams
Fat	3 grams
Percent of Calories from Fat	73%
Polyunsaturated Fat	1 gram
Saturated Fat	0 grams
Cholesterol (Δ)	0 mg (0 mg/100g)

In addition to the pint and quart size found in the dairy case of most grocery stores, Mocha Mix is available in 4 ounce and ½ oz. portion packs for hospitals and institutions.

Interested? Send us a note and we will send you a supply of coupons your patients can redeem at their grocers. Hospital service may also be supplied upon request. Mail to: Mocha Mix Dept. Presto Food Products, Inc. P.O. Box No. 21908, Los Angeles, Calif. 90021

Percentage of U.S. Recommended Daily Allowance (U.S. RDA) *

*Contains less than 2% of the U.S. RDA of Protein, Vitamin A, Vitamin C, Thiamine, Riboflavin, Niacin, Calcium, Iron.

ΔInformation on fat and cholesterol content is provided for individuals who, on the advice of a physician, are modifying their total dietary intake of fat and cholesterol.

mocha mix®

20 days to shape his world

In essential hypertension, the first 20 days are decisive.

The sad fact is, half of America's hypertensives drop out of treatment.[1]

You can improve those odds. Here's how:

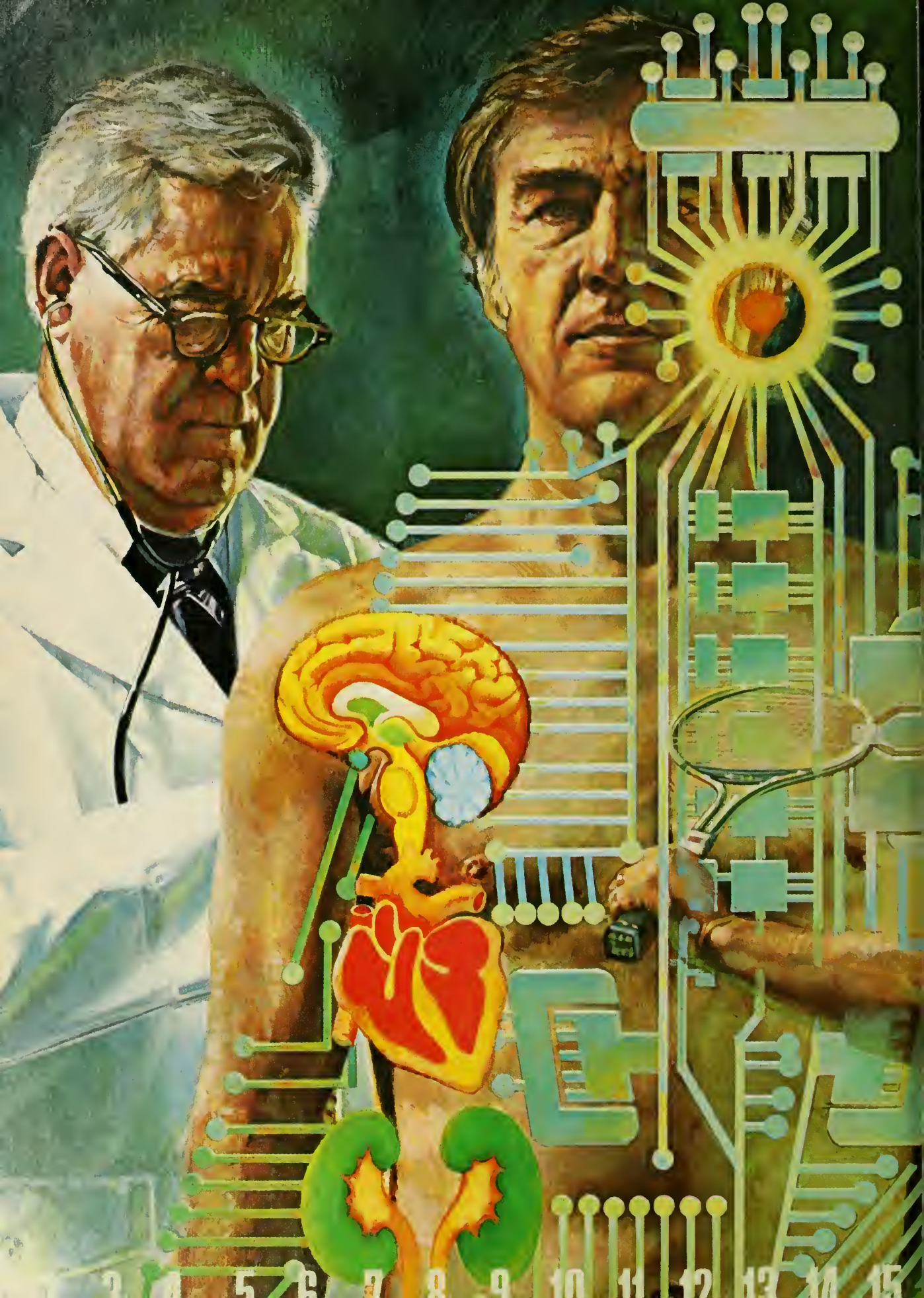
1. COUNSEL: Talk to your patient about the disease and its consequences—about strokes, heart attacks, and kidney failure. Tell him he *must* take medication daily, and for the rest of his life.

2. CATAPRES® (clonidine hydrochloride): because it works, and people stay with it.[2]

Counsel...and Catapres. They can help change the odds against your patient's future.

Please see brief summary of prescribing information on last page of this advertisement for warnings, precautions, and adverse reactions.

1.



Tablets of 0.1 and 0.2 mg

Catapres® (clonidine HCl) can help you shape his world

If you've come to expect only this much of Catapres...

1. smooth lowering of blood pressure
2. effective for all degrees of hypertension (mild to moderate in potency)
3. brain, heart, and kidney blood flow preserved

Ask for more of Catapres

1. no contraindications
2. normal hemodynamics
3. low incidence of depression and orthostatic hypotension
4. no fatal hepatotoxicity
5. excellent record of compliance

Most common side effects are dry mouth, drowsiness and sedation, which generally tend to diminish with time.

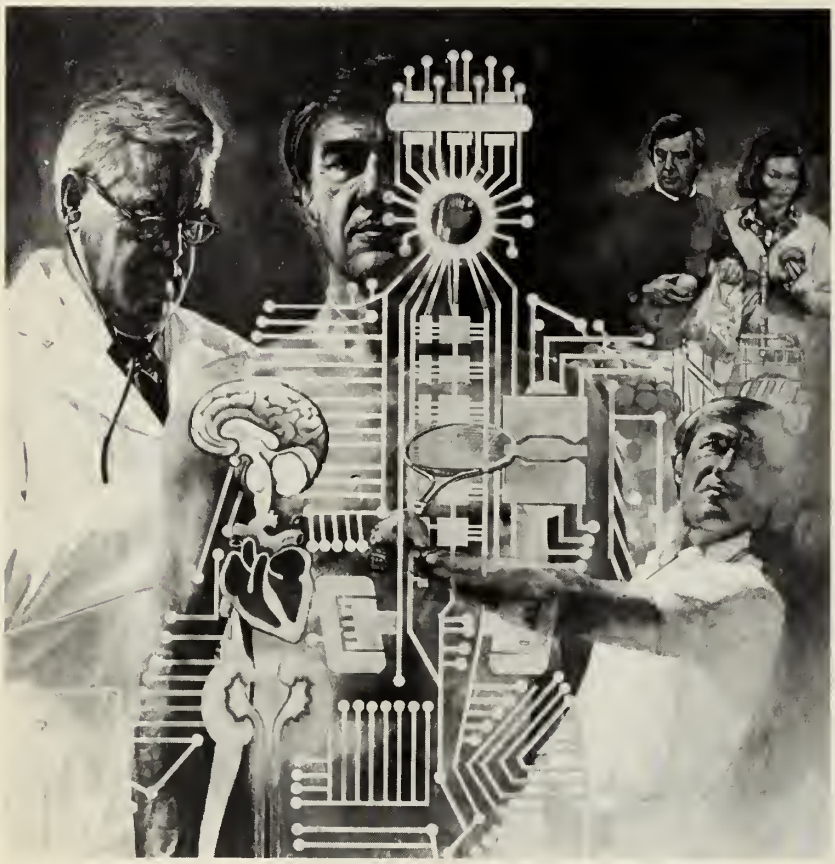
Please see brief summary of prescribing information on last page of this advertisement for warnings, precautions, and adverse reactions.

Tablets of 0.1 and 0.2 mg

Catapres® (clonidine HCl)

Hypertension

19 20 21 22 23 24 25 26 27 28 29 30 31



Tablets of 0.1 and 0.2 mg

Catapres® (clonidine HCl) can help you shape his world

Counsel...and Catapres. They can help change the odds against your patient's future. And to change them even more, ask us for these from your Boehringer representative:

— A major new film "Compliance: State of the Art"
— A compliance monograph
— Patient Aid Booklet
— Patient Worksheets
— Patient Reminder Postcards
— Other effective compliance enhancers

References:
1. Wilber JA, Barrow JS: Am J Med, *52*:653-663, 1972.
2. Data on file at Boehringer Ingelheim Ltd.

Boehringer Ingelheim

Catapres®
(clonidine hydrochloride)
Tablets of 0.1 mg and 0.2 mg

Indication: The drug is indicated in the treatment of hypertension. As an antihypertensive drug, Catapres (clonidine hydrochloride) is mild to moderate in potency. It may be employed in a general treatment program with a diuretic and/or other antihypertensive agents as needed for proper patient response.

Warnings: Tolerance may develop in some patients necessitating a reevaluation of therapy.
Usage in Pregnancy: In view of embryotoxic findings in animals, and since information on possible adverse effects in pregnant women is limited to uncontrolled clinical data, the drug is not recommended in women who are or may become pregnant unless the potential benefits outweigh the potential risk to mother and fetus.
Usage in Children: No clinical experience is available with the use of Catapres (clonidine hydrochloride) in children.

Precautions: When discontinuing Catapres (clonidine hydrochloride), reduce the dose gradually over 2 to 4 days to avoid a possible rapid rise in blood pressure and associated subjective symptoms such as nervousness, agitation, and headache. Patients should be instructed not to discontinue therapy without consulting their physician. Rare instances of hypertensive encephalopathy and death have been recorded after cessation of clonidine hydrochloride therapy. A causal relationship has not been established in these cases. It has been demonstrated that an excessive rise in blood pressure, should it occur, can be reversed by resumption of clonidine hydrochloride therapy or by intravenous phentolamine. Patients who engage in potentially hazardous activities, such as operating machinery or driving, should be advised of the sedative effect. This drug may enhance the CNS-depressive effects of alcohol, barbiturates and other sedatives. Like any other agent lowering blood pressure, clonidine hydrochloride should be used with caution in patients with severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease or chronic renal failure.

As an integral part of their overall long-term care, patients treated with Catapres (clonidine hydrochloride) should receive periodic eye examinations. While, except for some dryness of the eyes, no drug-related abnormal ophthalmologic findings have been recorded with Catapres (clonidine hydrochloride), in several studies the drug produced a dose-dependent increase in the incidence and severity of spontaneously occurring retinal degeneration in albino rats treated for 6 months or longer.

Adverse Reactions: The most common reactions are dry mouth, drowsiness and sedation. Constipation, dizziness, headache, and fatigue have been reported. Generally these effects tend to diminish with continued therapy. The following reactions have been associated with the drug, some of them rarely. (In some instances an exact causal relationship has not been established.) These include: Anorexia, malaise, nausea, vomiting, parotid pain, mild transient abnormalities in liver function tests; one report of possible drug-induced hepatitis without icterus and hyperbilirubinemia in a patient receiving clonidine hydrochloride, chlorthalidone and papaverine hydrochloride. Weight gain, transient elevation of blood glucose, or serum creatine phosphokinase; congestive heart failure; Raynaud's phenomenon; vivid dreams or nightmares, insomnia, other behavioral changes; nervousness, restlessness, anxiety and mental depression. Also rash, angioneurotic edema, hives, urticaria, thinning of the hair, pruritus not associated with a rash, impotence, urinary retention, increased sensitivity to alcohol, dryness, itching or burning of the eyes, dryness of the nasal mucosa, pallor, gynecomastia, weakly positive Coombs' test, asymptomatic electrocardiographic abnormalities manifested as Wenckebach period or ventricular trigeminy.

Overdosage: Profound hypotension, weakness, somnolence, diminished or absent reflexes and vomiting followed the accidental ingestion of Catapres (clonidine hydrochloride) by several children from 19 months to 5 years of age. Gastric lavage and administration of an analeptic and vasopressor led to complete recovery within 24 hours. Tolazoline in intravenous doses of 10 mg at 30-minute intervals usually abolishes all effects of Catapres (clonidine hydrochloride) overdosage.

How Supplied: Catapres, brand of clonidine hydrochloride, is available as 0.1 mg (tan) and 0.2 mg (orange) oval, single-scored tablets in bottles of 100 and 1000.

For complete details, please see full prescribing information.

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Bank of America's Professional Practice Management (PPM) is a computerized billing service for physicians that compiles, processes, stuffs and mails your statements in a fraction of the time it now takes you.

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In Edema* or Hypertension* when potassium balance is a concern...

Potassium-Sparing

DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Makes Sense

In Edema

The triamterene in 'Dyazide' limits potassium loss and provides an additive diuretic effect to that of the hydrochlorothiazide component.

In Hypertension

As the hydrochlorothiazide in 'Dyazide' lowers blood pressure, the triamterene component limits potassium loss.

Serum K^+ and BUN should be checked periodically particularly in the elderly, diabetics, and those with suspected or confirmed renal insufficiency (see Warnings). If hyperkalemia develops, substitute a thiazide alone.

Before prescribing, see complete prescribing information in SK&F Co. literature or *PDR*. A brief summary follows:

* **WARNING**
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Watch for signs of impending coma in severe liver disease. If spironolactone is used concomitantly, determine serum K^+ frequently; both can cause K^+ retention and elevated serum K^+. Two deaths have been reported with such concomitant therapy (in one, recommended dosage was exceeded, in the other serum electrolytes were not properly monitored). Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with thiazides. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effect may be enhanced in postsympathectomy patients. Use cautiously in surgical patients. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 and 1000 capsules; Single Unit Packages of 100 (intended for institutional use only).

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HALOG® [HALCINONIDE]

Wherever the cutaneous lesion appears, there is an appropriate form of Halog.

C = Halog® Cream 0.1%
Halcinonide Cream 0.1%

Discoid lupus erythematosus

After 10 days

S = Halog® Solution 0.1%
Halcinonide Solution 0.1%

Seborrheic dermatitis

After 1 week

O = Halog® Ointment 0.1%
Halcinonide Ointment 0.1%

Psoriasis

After 1 week

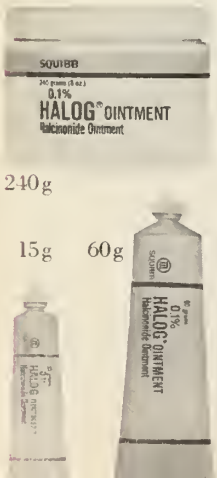
SQUIBB®

HALOG® [HALCINONIDE]

HALOG (Halcinonide) CREAM/OINTMENT/SOLUTION
Halog Cream 0.025% (Halcinonide Cream 0.025%) and Halog Cream 0.1% (Halcinonide Cream 0.1%) contain 0.25 mg and 1 mg halcinonide per gram, respectively, in a specially formulated cream base. Halog Ointment 0.1% (Halcinonide Ointment 0.1%) contains 1 mg halcinonide (0.1%) per gram in Plastibase® (Plasticized Hydrocarbon Gel), a polyethylene and mineral oil gel base. Halog Solution 0.1% (Halcinonide Solution 0.1%) contains 1 mg halcinonide (0.1%) per ml.
CONTRAINDICATION: Topical steroids are contraindicated in those patients with a history of hypersensitivity to any of the components of the preparations.
PRECAUTIONS:
General—If irritation develops, discontinue the product and institute appropriate therapy. In presence of an infection, institute use of a suitable antibacterial or antifungal agent. If a favorable response does not occur promptly, discontinue the corticosteroid until the infection has been adequately controlled. If extensive areas are treated or if the occlusive technique is used, there will be increased systemic absorption of the corticosteroid and suitable precautions should be taken, particularly in children and infants. These preparations are not for ophthalmic use.
Usage in Pregnancy—Although topical steroids have not been reported to have an adverse effect on human pregnancy, the safety of their use in pregnant women has not been absolutely established. In laboratory animals, increases in incidence of fetal abnormalities have been associated with exposure of gestating females to topical corticosteroids—in some cases at rather low dosage levels. Therefore, drugs of this class should not be used extensively on pregnant patients, in large amounts, or for prolonged periods of time.
Occlusive Dressing Technique—The use of occlusive dressing increases the percutaneous absorption of corticosteroids. For patients with extensive lesions it may be preferable to use a sequential approach, occluding one portion of the body at a time. Keep the patient under close observation if treated with the occlusive technique over large areas and over a considerable period of time. Occasionally, a patient who has been on prolonged therapy, especially occlusive therapy, may develop symptoms of steroid withdrawal when the medication is stopped. Thermal homeostasis may be impaired if large areas of the body are covered. Discontinue use of the occlusive dressing if elevation of the body temperature occurs.

Occasionally, a patient may develop a sensitivity reaction to a particular occlusive dressing material or adhesive and a substitute material may be necessary. If infection develops, discontinue the use of the occlusive dressing and institute appropriate antimicrobial therapy.
ADVERSE REACTIONS: The following local adverse reactions have been reported with topical corticosteroids, especially under occlusive dressings: burning sensations, itching, irritation, dryness, folliculitis, hypertrichosis, acneform eruptions, perioral dermatitis, allergic contact dermatitis, hypopigmentation, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.
For full prescribing information, consult package inserts.
HOW SUPPLIED: The 0.025% and 0.1% Cream and the 0.1% Ointment are supplied in tubes of 15 g and 60 g, and in jars of 240 g (8 oz). The 0.1% Solution is supplied in plastic squeeze bottles of 20 ml and 60 ml.

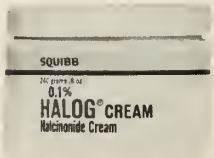
Halog Ointment 0.1%
Halcinonide Ointment 0.1%



240 g

15 g 60 g

Halog Cream 0.1%
Halcinonide Cream 0.1%



240 g

15 g 60 g

Halog Cream 0.025%
Halcinonide Cream 0.025%

240 g

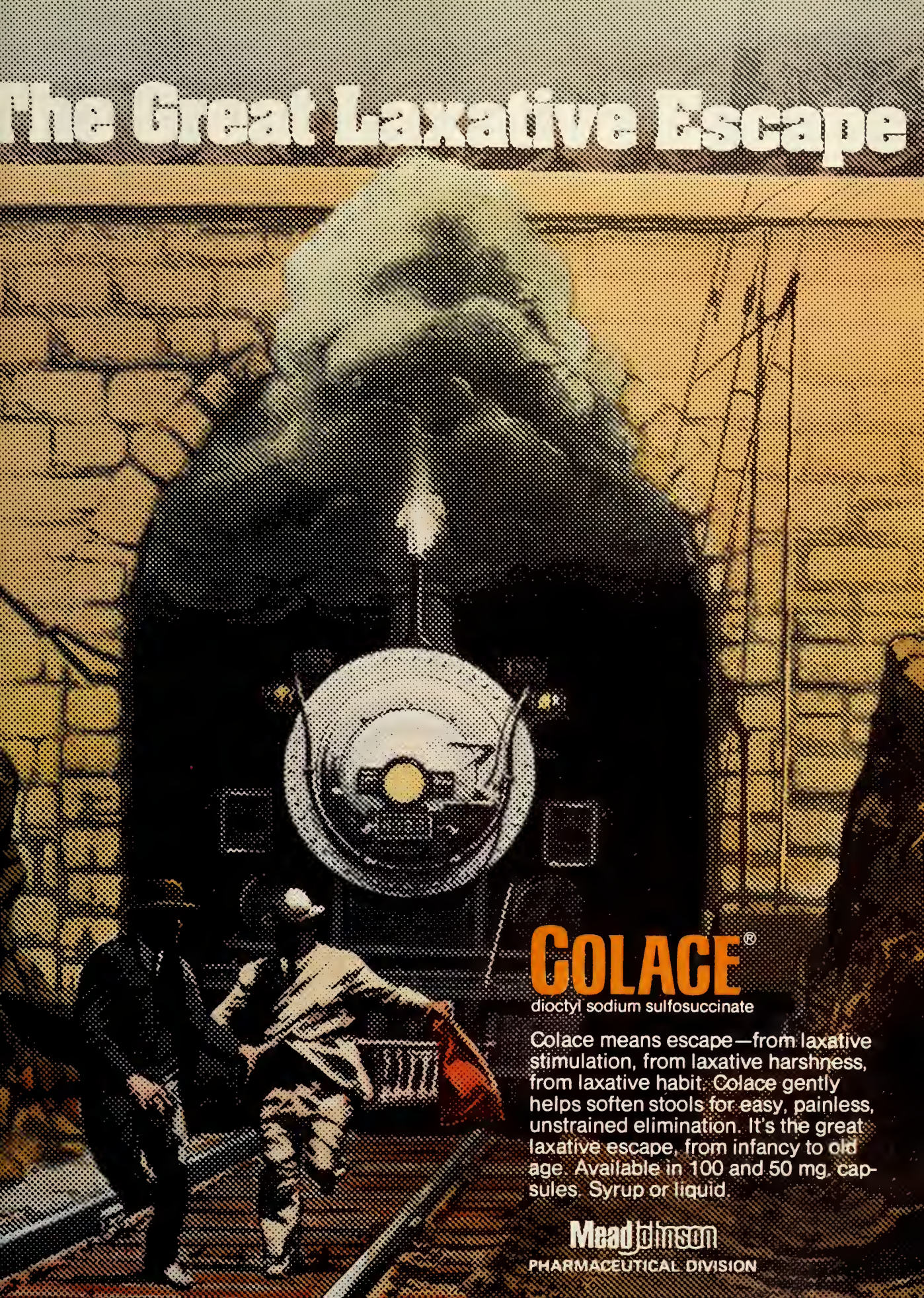
15 g 60 g

Halog Solution 0.1%
Halcinonide Solution 0.1%

20 ml

60 ml

The Great Laxative Escape



COLACE®
dioctyl sodium sulfosuccinate

Colace means escape—from laxative stimulation, from laxative harshness, from laxative habit. Colace gently helps soften stools for easy, painless, unstrained elimination. It's the great laxative escape, from infancy to old age. Available in 100 and 50 mg. capsules. Syrup or liquid.

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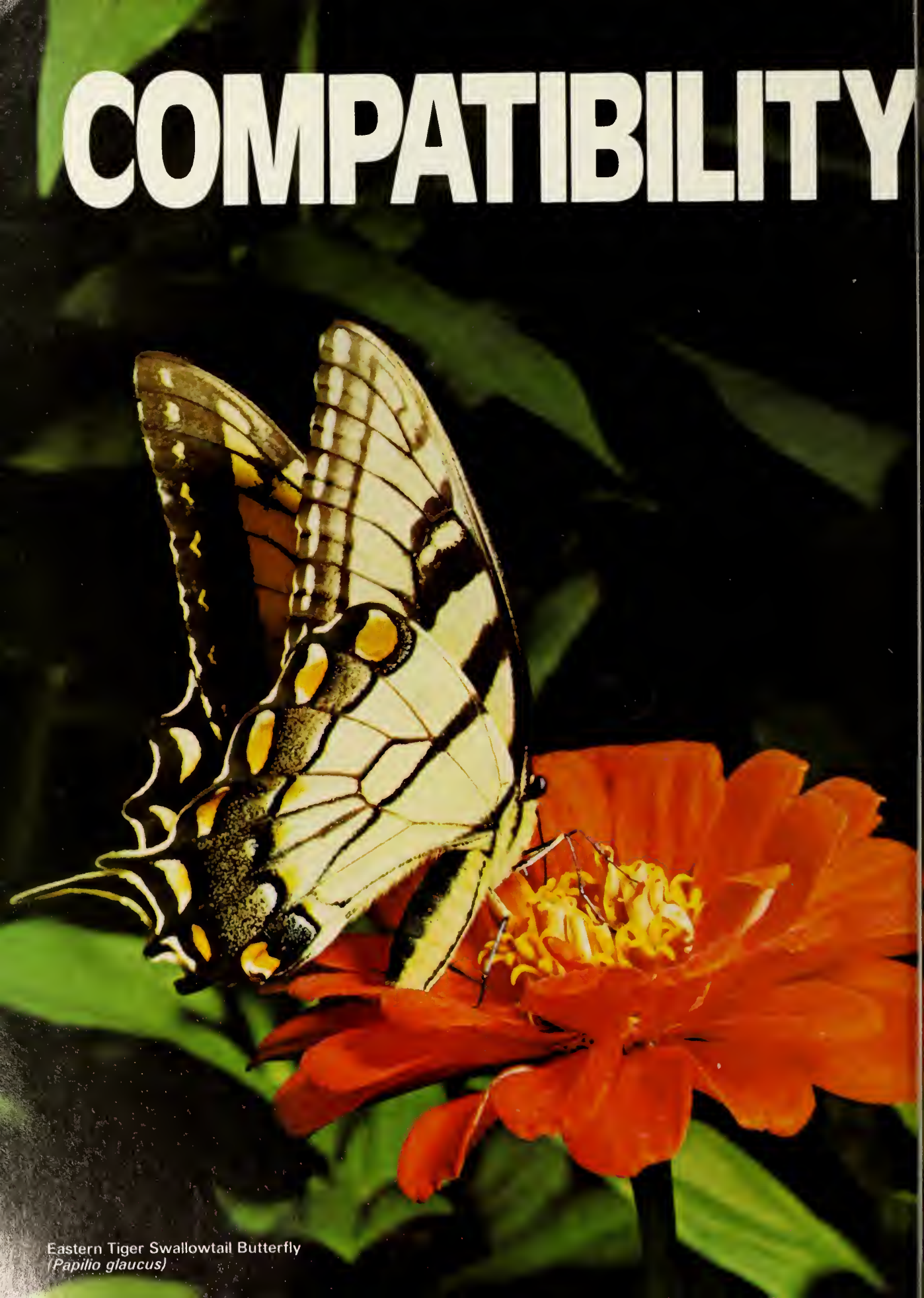
COMPATIBILITY



Eastern Tiger Swallowtail Butterfly
(Papilio glaucus)

Does it influence your choice of a peripheral/cerebral vasodilator*?

Vasodilan–compatible with coexisting diseases (e.g., glaucoma, diabetes)

Vasodilan has not been reported to affect the course of coexisting disease; it has not been reported to affect blood sugar levels or to raise intraocular pressure.

Vasodilan–compatible with concomitant therapy

Vasodilan has not been reported to affect the treatment of coexisting disease; it is compatible with such drugs as hypoglycemics and miotics.

Vasodilan–compatible with your total regimen for vascular insufficiency

Vasodilan can be a valuable adjunct in planning a total therapeutic program for vascular insufficiency.

***Indications:** Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, the FDA has classified the indications as follows:

Possibly Effective:

1. For the relief of symptoms associated with cerebral vascular insufficiency.
2. In peripheral vascular disease of arteriosclerosis obliterans, thromboangiitis obliterans (Buerger's Disease) and Raynaud's disease.

Final classification of the less-than-effective indications requires further investigation.

Composition: Vasodilan tablets, isoxsuprine HCl, 10 mg. and 20 mg.
Vasodilan injection, isoxsuprine HCl, 5 mg., per ml.

Dosage and Administration: Oral: 10 to 20 mg., three or four times daily.
Intramuscular: 5 to 10 mg.(1 or 2 ml.) two or three times daily. Intramuscular administration may be used initially in severe or acute conditions.

Contraindications and Cautions: There are no known contraindications to oral use when administered in recommended doses. Should not be given immediately postpartum or in the presence of arterial bleeding.

Parenteral administration is not recommended in the presence of hypotension or tachycardia.

Intravenous administration should not be given because of increased likelihood of side effects.

Adverse Reactions: On rare occasions oral administration of the drug has been associated in time with the occurrence of hypotension, tachycardia, nausea, vomiting, dizziness, abdominal distress, and severe rash. If rash appears the drug should be discontinued.

Although available evidence suggests a temporal association of these reactions with isoxsuprine, a causal relationship can be neither confirmed nor refuted

Administration of single dose of 10 mg. intramuscularly may result in hypotension and tachycardia. These symptoms are more pronounced in higher doses. For these reasons single intramuscular doses exceeding 10 mg. are not recommended. Repeated administration of 5 to 10 mg. intramuscularly at suitable intervals may be employed

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Epidemiology of Waterskiing Injuries

JOHN V. BANTA, MD, *San Diego*

Coast Guard statistics indicate a national boating fatality rate of 9.6 deaths per 100,000 crafts. In 1977 in California, five fatalities and 70 serious injuries were directly attributable to waterskiing. The four cases reported here include three patients with propeller injuries, including one nearly fatal amputation. In each case basic measures for boating safety were overlooked.

Skiers in Minnesota in 1922[1] and in Washington state in 1928[2] have been credited with first adapting their snow skis to waterskiing. The popularity of waterskiing has risen dramatically in the past decade, influenced in part by a general reduction in the length of the average work week, coupled with a notable rise in the number of propeller-driven small craft. According to the latest edition of *Coast Guard Boating Statistics*,[3] the overall fatality rate for boating injuries per 100,000 persons declined from 20.8 in 1961 to 9.6 in 1977. However, the estimated number of boats afloat rose from 5.85 million to 13.6 million in the same time. Fatalities attributable to waterskiing in the United States in 1977 totaled 43. During the same year five fatalities and 70 serious injuries directly involving water-skiers were registered in California (personal communcations, Mr. Harvey H. Houk, Supervisor of the Enforcement Unit, State of California Department of Navigation and Ocean Development). The following four cases of serious waterskiing injuries treated in a community hospital near San Diego Bay during the past four years illustrate the potentially serious hazards associated with this recreational activity.

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Submitted October 26, 1978.

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Reports of Cases

Case 1. Two girls were swimming in San Diego Bay when one girl attempted to dive beneath an oncoming boat that was towing a waterskier. The trunk of the patient was submerged; however, both buttocks received serial lacerations of the skin and subcutaneous tissues from the propeller. After initial evaluation in the emergency room, surgical repair was done under general anesthesia. The lacerations penetrated to, but did not involve, the gluteal musculature. Debridement, closure over drains, and prophylactic antibiotic administration for 96 hours resulted in primary healing of wounds with no sequelae.

Case 2. The second of the two girls was struck by the same propeller and received massive lacerations involving both buttocks, and presacral and right thigh regions (Figure 1). Fluids were given intravenously, and blood was typed and crossmatched for replacement. On physical examination an open transverse subtrochanteric fracture of the right femur, anesthesia and motor loss distal to the knee were noted (Figure 2). The right gluteal wound penetrated to the ischial tuberosity with exposure and partial laceration of

Figure 1.—(Case 2) Massive serial gluteal and thigh lacerations from a propeller. The patient is an 8-year-old-girl who attempted to dive beneath an oncoming boat that was towing a water-skier.

the sciatic nerve. The bladder was catheterized, resulting in prompt return of clear urine.

During surgical operation all wounds were debrided with copious irrigations supplemented with bactracin and kanamycin sulfate (Kantrex) solution. The sciatic nerve laceration involved the posterior 20 percent of the nerve immediately adjacent to the superior aspect of the ischial tuberosity. Epineural repair was carried out and all wounds were loosely approximated over large Penrose drains. The patient was turned to a supine position and the femoral fracture was treated in skeletal traction in a 90-90 overhead position. A similar means of traction for the uninvolved left leg allowed suspension of the lower trunk and buttocks for appropriate wound and perineal care. After four weeks all wounds had healed except for one area of the right buttock that required split-thickness skin grafting.

In the sixth week the patient was placed in a double spica cast and was discharged eight weeks following the injury. In the 12th week the patient's spica cast was removed, and trace function of the gastrosoleus, flexor hallucis and flexor digitorum comminis muscles was noted. The patient was allowed to use crutches with a polypropylene orthosis for the ankle and foot; she resumed walking without crutches six months after injury. Nine months after the injury, results of electromyographic examination showed electrical activity in the gastrocnemius and anterior tibial and peroneal muscles. After ten months anterior tibial and peroneal muscle function was clinically detectable. Complete protective sensation and proprioceptor response returned after 14 months and, following 16 weeks of serial short leg-stretching casts, a heel cord contracture of 10 degrees was overcome. The patient was then discharged from care 24 months after injury. She could walk without assistance, and there was normal motor and sensory function of the right leg.

Case 3. A 56-year-old woman, a water-ski instructor with 25 years of experience, was demonstrating a "from the beach start" for a class of beginning water-skiers when her left leg became entangled in the tow rope. Her husband, who was piloting the boat, immediately cut the throttle. Nonetheless, the woman was pulled forward with her foot locked into the ski; this caused a pronation external rotation grade 3 dislocation fracture of the ankle (Figure 3). The woman's wet suit protected her skin, which had only partial thick-

Figure 2.—(Case 2) Anteroposterior roentgenogram made on the patient's admission to hospital. Open subtrochanteric fracture of the right femur is shown. A 20 percent transection of the sciatic nerve occurred at the level of the ischial tuberosity.

ness abrasions of the epithelium. Surgical repair of the deltoid ligament with internal fixation of the fibular malleolus was immediately begun

Figure 3.—(Case 3) Initial x-ray film of a pronation external rotation grade 3 dislocation fracture of the ankle that occurred when a water-ski instructor was caught in a tow rope while demonstrating a take-off from the beach.

Figure 4.—(Case 3) Roentgenogram made following surgical repair of the deltoid ligament and fixation of the fibular fracture. A sewing needle shown in the anterior soft tissue of the distal pretibial area is not related to the waterskiing injury.

Figure 5.—(Case 4) A 31-year-old woman, preparing to water ski, was struck by a boat. There was complete amputation of the left leg and transection of the soft tissues of the posterior aspect of the right thigh excluding the femur, femoral vessels and sciatic nerve.

(Figure 4). The patient's convalescence was uneventful and she returned to recreational skiing nine months after the injury.

CASE 4. A 31-year-old woman, preparing to water ski, was submerged at the stern of a boat when it was suddenly reversed and backed down upon her. The left leg and thigh were amputated, and severe propeller lacerations of the right thigh occurred before the woman could be pulled into the boat. Pressure pack dressings were applied to the pelvic area and the patient was transported by a police ambulance to the emergency room. The patient was conscious with no obtainable blood pressure. Following resuscitation measures and fluid replacement, physical examination showed complete avulsion of the left sacroiliac joint with the ilium lying free on a pedicle flap of the iliac muscle. The left femoral artery was stretched from its surrounding muscle and was in spasm with no active bleeding. The posterior aspect of the right thigh had a deep propeller laceration extending from the pectineal muscles posteriorly with transection of the medial hamstring and adductor musculature, and with no injury of the femur, iliac vessels and sciatic nerve (Figure 5).

A hip disarticulation was carried out in the left pelvic region and the iliac bone was secured with Steinmann pins. After extensive soft tissue debridement, the posterior gluteal flap was loosely closed over a large number of Penrose drains. The right thigh wound, after debridement, was simi-

larly closed loosely after repair of the adductor and hamstring musculature (Figure 6).

The patient's convalescence was prolonged and complicated by the development of a mixed aerobic and anaerobic necrotizing synergistic infection with cultures of Gram-positive cocci, clostridia, bacteroides and aerobic Gram-negative bacilli. Antibiotic therapy included cephalothin sodium (Keflin), penicillin, clindamycin and gentamycin. The patient was returned to surgery five days after injury so that intermittent suction irrigation systems could be used, and further debridement of necrotic tissue could be carried out. Further necrotic tissue was debrided 11 days after injury. Profuse arterial bleeding from the depths of the wound adjacent to the acetabulum was controlled by vaginal packs and during the next eight weeks all major wounds healed except a chronic sinus tract adjacent to the acetabulum (Figure 7). The patient regained full use of the right leg and was discharged on crutches three months after injury.

She returned to the hospital four months after the injury for resection of an avascular segment of the ilium; the wound healed completely (Figure 8). She was fitted with a Canadian type hip

Figure 6.—(Case 4) Posterior view of propeller lacerations following hip disarticulation and wound closure.

Figure 7.—(Case 4) Anteroposterior view of the pelvis on the patient's admission to hospital showing bilateral pubic fractures and complete disruption of the left acetabulum and ilium, in addition to subtrochanteric amputation of the left femur.

Figure 8.—(Case 4) Shown are anteroposterior views of the pelvis one and two months following injury **(upper)**, initial fixation of the pelvis and **(lower)**, subsequent excision of avascular iliac fragment.

disarticulation prosthesis six months after injury and returned to work as an accountant nine months after injury.

Discussion

Stanisauljevic recently reviewed the causes of orthopedic injuries similar to those in case 3 in this series and identified several related factors including the inexperience of water-skiers and pilots, and excessive boat speed. He estimated that more than 2 million people water-ski in the United States. McCarthy[4] reported a case in which a young woman fell while skiing and received a 5-cm laceration in the fornix vaginae. Ramey[5] reported the case of a young woman who fell while skiing, which resulted in an intrarectal tear with profuse hemorrhage. Both of these cases involved women wearing brief swimming suits and the authors speculate that the use of more protective apparel, such as wet suits, might have precluded severe injuries.

Three of the four cases were directly attributable to deficient boat handling. The third case would have involved open fracture or possible amputation were it not for the prompt attention of the driver.

The most devastating injuries, however, are caused by propellers, as is well-documented by Mann.[6] In his series of nine cases from Miami there were three deaths and three amputations. Propeller injuries usually result in a series of transverse incisions as each blade sequentially strikes further up the victim's body as illustrated by the photographs. In addition to the frequent massive soft tissue and bone injuries, there is the threat of severe wound infections from bacterial contamination. Case 4 illustrates the catastrophic nature of propeller injuries and the problems of subsequent infection in spite of radical debridement, extensive drainage and broad spectrum antibiotic therapy. These propeller injuries are the civilian equivalent of severe battlefield injuries.

Analysis of the 1977 California waterskiing injury statistics[4] shows that of five skiers who were killed, two skiers struck rocks, two were struck by the boat, and one lost the ski belt and subsequently drowned. The 70 injuries reported could be classified according to causes shown in Table 1.

TABLE 1.—*Causes of Waterskiing Injuries in California in 1977*

Fall	17
Tow line	13
Boat	10
Ski	7
Propeller	7
Beach	6
Rocks	5
Trees, logs	2
Buoy	2
Bridge	1
	70

As shown by a review of the United States *Coast Guard Boating Statistics,* waterskiing fatalities rose from 34 in 1976 to 43 in 1977. There is evidence that an increase in population with overcrowding of available water space in the San Diego Bay area, resulting in inadequate separation of boating and bathing areas, was a significant factor in two of the four cases reported here.

Conclusions

With the increasing popularity of waterskiing, records of injuries are showing increases in total incidence and fatalities. Education of both skiers and drivers could reduce substantially the incidence of serious injury. Accidents involving propellers remain the chief cause of devastating and mutilating injuries. Medical treatment of these catastrophic injuries should be comparable to the treatment of massive battle wounds, with adequate debridement and secondary closure techniques in addition to appropriate antibiotic therapy.

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Antibiotic Use in a Small Community Hospital

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Audits of medical records were done for similar one-month periods in 1974 and 1977 in a 125-bed community hospital in Hawaii to determine patterns of antibiotic use. One quarter of all hospital patients in both study periods received antibiotics. In 1977 cephalosporins, ampicillin and aminoglycosides were the most commonly used antibiotics. Half of the antibiotics used by surgical specialty departments in both periods were for prophylactic indications. The cost of antimicrobial prophylaxis per patient was reduced by about 57 percent in 1977 compared with 1974. In the 1977 period, 58 percent of patients received proper prophylactic antibiotic regimens; this was statistically higher than the 15 percent of patients given appropriate prophylactic antibiotics in 1974. Fewer than half of the patients in both study periods treated for infections received correct antibiotic therapy. In contrast, 82 percent of infectious disease consultations were considered appropriate by an independent specialist in infectious disease. However, these consultations were obtained in only 15 percent of the patients who received therapeutic antibiotics. It was concluded that audits of patients receiving antibiotics can be effective in the development of appropriate prophylactic surgical regimens. However, during the study period in 1977, we were not able to show large scale improvement in therapeutic antimicrobial use at this community hospital, either by our attempts at physican education or by making infectious disease consultations available.

ANTIBIOTICS are the most commonly prescribed drugs, and approximately 25 percent of all patients admitted to hospital receive antibiotic therapy.[1] Hospital Accreditation Standards on Infection Control established by the Joint Commission on Accreditation of Hospitals now include "the regular review of clinical usage of antibiotics."[2] A committee of experts from the American Medical Association has made preliminary recommendations that each hospital should monitor antibiotic use, develop guidelines for appropriate use of antibiotics, distribute such guidelines to its medical staff and have a consultant review antibiotic use annually.

In 1979 Scheckler and Bennett conducted surveys in seven community hospitals and reported that in 62 percent of all patients who received antibiotics there was no recorded evidence of in-

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fection.[3] In 1972 Roberts and Visconti reported that 87 percent of patients in a single community hospital received either "irrational" or "questionable" therapy.[4] Since these studies, several evaluations of *appropriate* antibiotic usage have been done in large academic centers, using carefully devised categories of performance.[5-7] In 1974 and 1977 we used such criteria to evaluate the use of antibiotics in a community hospital in Hawaii.

Methods

To determine prevailing antibiotic usage patterns, a retrospective audit was done of patients in a 125-bed community hospital who received antibiotic therapy and were discharged during a month in 1974. Information was obtained regarding the type of antibiotic, dosage, duration, cost and reasons for therapy. Prophylactic antibiotic therapy was defined as the use of antimicrobial agents in uninfected patients in the hope of preventing infectious complications often associated with instrumentation or a surgical procedure. These patients had no fever, leukocytosis (greater than 10,000 leukocytes per cu mm) or clinical suspicion of having infected lesions.[8]

Initially, what constituted *appropriate* prophylactic antibiotic use was decided in January 1975 on the basis of a review of medical literature concerning each surgical procedure; these assessments were reviewed again in 1978 using the criteria of the Veterans Administration Ad Hoc Interdisciplinary Advisory Committee on Antimicrobial Drug Use[8,9] and a study of prophylactic antibiotics in orthopedic surgery by Pavel and coworkers.[10] Use of *therapeutic* antibiotics was classified by categories suggested by Kunin and co-workers:[5] (I) agree with antimicrobial therapy as appropriate; (II) agree with antimicrobial therapy because a potentially fatal bacterial infection cannot be ruled out; (III) agree with the use of antimicrobial therapy, but a different (usually less expensive or toxic) antimicrobial is preferred; (IV) agree with the use of antimicrobial therapy, but a modified dose is recommended; (V) use of antibiotic therapy is unjustified.

During the latter half of 1975 results of this initial study were given orally and in writing to each hospital department at one of their monthly meetings. Proper antibiotic use in specific cases was discussed and cost of each antibiotic was emphasized. A detailed list of references concerning prophylactic antibiotic usage was prepared for each surgical department and antibiotic guidelines for various procedures were determined cooperatively. Several lectures on antibiotic treatment of infectious problems were given to both attending and resident staff physicians. Also, beginning in 1975, infectious disease consultations in the hospital were available anytime by request of attending physicians. There were no drug restrictions or microbial culture requirements.

After three years, another audit was done of medical records of all patients receiving antibiotics who were discharged during a month in 1977. The senior author reviewed retrospectively prophylactic use of antibiotics, using the 1974 criteria. An infectious disease consultant (W.L.), with no cases at this hospital, reviewed all therapeutic use of antibiotics with the criteria previously described. Statistical differences in antibiotic use for the two study periods were determined by chi-square analysis.

Results

General Patterns of Antibiotic Usage

Table 1 shows the comparative prevalence of antibiotic use by hospital services in 1974 and 1977. In 1974 it was found that 24 percent (99

TABLE 1.—*Antibiotic Use by Hospital Service*

Hospital Service	Percent of Patients Receiving Antibiotics Compared to Total Hospital Patients in Each Service		Percent of Prophylactic Antibiotic Use Compared to Total Antibiotic Use in Each Service	
	1974	1977	1974	1977
Medicine	22	19	20	2
Surgery/gynecology	26	33	62	57
All services	24	27	55	41

TABLE 2.—*Use of Individual Antibiotics*

Antibiotic	Percent of Total Antibiotic Orders		Percent of Prophylactic Use Compared to Total Use	
	1974	1977	1974	1977
Ampicillin	28	21	32	27
Cephalosporins	16	30	50	52
Tetracyclines	12	6	27	17
Urinary antibiotics (sulfonamides, nitrofurantoin)	14	4	50	50
Clindamycin	7	4	33	0
Erythromycin	7	6	83	58
Penicillins (including semisynthetic)	6	7	40	38
Aminoglycosides (gentamicin, tobramycin, kanamycin, neomycin)	9	20	11	23
Chloramphenicol	1	2	0	33

patients) of all discharged patients received antibiotic therapy. In 1977, however, 27 percent (154 patients) received antibiotic therapy. Total prophylactic use of antibiotics in the month in 1977 was somewhat lower than the period in 1974 (41 percent versus 55 percent); however, this was not statistically significant ($p<.10$). When analyzed by department, it was found that certain surgical specialties (orthopedics, general surgery, cardiovascular surgery, thoracic surgery, urology and plastic surgery) used antibiotics in 40 percent to 50 percent of their patients—twice as frequently as in the medical department. As shown in Table 1, the increase in frequency was primarily the result of a high incidence of surgical prophylaxis.

Table 2 shows a comparison of the antibiotic classes most commonly used in the two study periods. Ampicillin, cephalosporins and tetracycline were among the most common drugs used in 1974. In 1977 a third of the antibiotics ordered were cephalosporins; in half of these instances the drugs were used prophylactically. Only 9 percent of the antibiotics ordered in 1974 were aminoglycosides; this increased to 20 percent in 1977.

TABLE 3.—*Cost of Antibiotic Medications to Patients*

	Therapeutic Antibiotic Cost (dollars per patient)*		*Prophylactic Antibiotic Cost* (dollars per patient)*	
Hospital Service	*1974*	*1977*	*1974*	*1977*
Medicine	47	140	34	16
Surgery/gynecology	30	78	53	21
All services	54	96	47	20

*Calculated with December 1974 drug prices

Table 3 indicates the cost to hospital patients of antibiotic therapy during our study periods, based on prevailing prices in December 1974. The cost of prophylactic antibiotics in 1977 was $20 per patient, less than half the cost in 1974. The cost per patient for therapeutic antibiotics increased from $54 in 1974 to $96 in 1977. This increase was seen in all three services of the community hospital.

Appropriateness of Prophylactic Use

Table 4 compares the prophylactic use of antibiotics in 1974 and in 1977. In 1974 only 15 percent of patients were considered to be receiving appropriate prophylactic antibiotic regimens, compared with 58 percent in 1977. This was a statistically significant improvement ($p\leq.001$), primarily seen in cardiovascular, gynecological and general surgical services. There was no statistical differences between patients treated for inappropriate indications and those treated with an improper choice of antibiotic. The major difference was in the antibiotic regmens; only 4 percent of patients in 1977 did not have prophylactic antibiotics started prior to or during their surgical procedure, compared to 32 percent in 1974 ($p\leq.001$). Also, most postoperative treatment periods were shortened to 8 to 72 hours, depending on the nature of the procedure.

Appropriateness of Therapeutic Use of Antibiotics

Table 5 compares therapeutic use of antibiotics in the two study periods. In 1974 it was found that 45 percent of infections were treated appro-

TABLE 4.—*Patterns of Prophylactic Antibiotic Use*

	Number of Patients Treated Prophylactically		*Percent of Patients Receiving Appropriate Prophylactic Antibiotic Therapy*		*Percent of Patients Treated for Inappropriate Prophylactic Indications or With Improper Antibiotics*		*Percent of Cases With Only Wrong Timing in Antibiotic Administrations*	
Hospital Service	*1974*	*1977*	*1974*	*1977*	*1974*	*1977*	*1974*	*1977*
Medicine	7	1	0	100	0	0	0	0
Gynecology	9	2	0	100	13	0	87	0
Cardiovascular surgery	2	7	0	100	0	0	100	0
General surgery	4	7	25	56	75	42	0	0
Orthopedic surgery	5	15	80	93	20	7	0	0
Urology	5	10	0	20	100	80	0	0
Other surgical subspecialties (ear, nose, and throat; plastic surgery, thoracic surgery, neurosurgery)	9	13	12	15	55	70	33	15
All services	41	55	15	58	53	38	32	4

TABLE 5.—*Patterns of Therapeutic Antibiotic Use*

Hospital Service	Number of Infections Treated for Therapeutic Indications		Percent of Infections in Categories									
			Appropriate				Inappropriate					
			I		II		III		IV		V	
	1974	1977	1974	1977	1974	1977	1974	1977	1974	1977	1974	1977
Medicine	28	51	32	35	11	15	39	29	0	15	18	8
Surgery/gynecology	29	38	48	34	0	8	35	29	10	13	7	16
All services	57	89	40	35	5	11	38	29	5	15	12	11

priately (Kunin's categories I and II, as previously discussed). In 1977, 46 percent of patients with infections received appropriate antibiotic therapy. There were no significant differences in these percentages or in the other categories.

Effectiveness of Infectious Disease Consultation

During 1977 only 11 (15 percent) of the 75 patients who received therapeutic antibiotic therapy had consultations with a specialist in infectious disease. The recommendations made by the consultant resulted in antibiotic regimen changes beneficial to patient care in nine of the 11 (82 percent) cases assessed by an independent specialist in infectious disease. The antibiotic regimens were considered unsatisfactory (categories III and IV) in the remaining two cases. In six of the infectious disease consultations, the patient's initial antibiotic therapy was changed from an *inappropriate* category (III or IV) to an *acceptable* one (I or II).

Discussion

Recently, great emphasis has been placed on correcting the misuse of antibiotics to avoid adverse reactions, reduce bacterial drug resistance, decrease patient cost and possibly reduce the rate of superinfection. Kunin and co-workers[5] reported that in 1969 a three-month study of antibiotic use at the University of Virginia hospital showed that 27 percent of medical patients and 29 percent of surgical patients received antibiotics. In that study, 58 percent of the surgical patients and 6 percent of the medical patients were given antibiotics for prophylactic indications. In 61 percent of the surgical cases and in 42 percent of the medical cases therapy was considered inappropriate (categories III to V). A similar study at Duke University Medical Center in 1973 indicated that 64 percent of antibiotic use was inappropriate, due primarily to errors in surgical prophylaxis; only 19 percent of therapeutic antibiotics therapy given to medical patients was considered inappropriate.[6] Jones and associates[7] placed 45 percent of all treated patients at the Dallas Veterans Administration Hospital in *inappropriate* or *unjustified* category, even after six months of intensive physician education.

The frequency and distribution of individual antimicrobial usage in our study was similar to that in previously published reports.[3-7] We found in our initial evaluation in 1974 that only 15 percent of prophylactic antibiotics and 45 percent of therapeutic antibiotics were used appropriately. Because our study was done in a private community hospital, we felt that previously described restrictive measures, such as required consultations[5,11] or formulary control were not practical. Also, as was suggested by Counts, ideally physician education should be the first factor in controlling antibiotic usage.[12]

Our attempts at physician education were well received. Each surgical service welcomed a review of the scientific literature for indications and antimicrobial regimens currently recommended for prophylaxis. Standardized antibiotic regimens were collaboratively designed for various surgical procedures in cardiovascular, orthopedic and gynecological surgery. These measures greatly improved prophylactic antibiotic use in 1977. In addition, because antimicrobial regimens were significantly shortened, the cost of prophylactic antibiotics per patient in 1977 was reduced to less than half the cost in 1974 (Table 3).

In contrast, we found no improvement between the two study periods in the use of therapeutic antimicrobial agents, despite educational lectures and infectious disease consultations. The cost of therapeutic antibiotics increased dramatically in 1977, partially because of more frequent and prolonged use of cephalosporins and aminoglycosides (Table 2). More important, there was no difference in the total percentage of appropriate treatments for infections in the two study periods (45 percent versus 46 percent). Although physicians welcomed information on the proper selection of

antibiotics, they were not able to apply this information properly to most patients treated for infection. This can be explained by the large number of new antibiotics, the complexities of microbiological diagnosis and the extensive literature concerning treatment of different infectious diseases. In spite of these factors, these physicians used infectious disease consultations rather sparingly: in 15 percent of therapeutic cases in this study. As a result of consultations, the antibiotic regimens of several seriously ill patients were changed from *inappropriate* categories to *appropriate* ones.

The clinical significance of this study is not clear; a much larger audit based on patient outcome would be required. Many of the patients who received therapeutic antibiotic therapy were treated for mild infections. The efficacy of prophylactic regimens of antibiotics is largely undetermined for *clean* cardiac or orthopedic surgical procedures. However, our judgment of proper antibiotic use was based on extensive published experiences with therapeutic and prophylactic antimicrobial use. Therefore, *correct* antibiotic therapy should ultimately be highly beneficial to all hospital patients receiving antimicrobial drugs.

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Acupuncture as a Placebo

IT'S THOUGHT PROVOKING to evaluate our competitors and, in the recent past, acupuncture has been something that has been considered a very effective competitor of the physician, at least in some cultures. . . . Would the acupunctures do almost as well with a lot of our patients as we do? . . . I think it is fair to say, without even tongue in check, that 35 percent of the patients that come into your office or mine would be substantially benefitted—a lot of them even would be cured in a month or two—with almost any eye problem. . . . There are a lot of different kinds of placebo therapy. . . . Every action that you take upon a patient has a placebo effect in addition to a specific effect.

—WILLIAM H. HAVENER, MD, *Columbus, Ohio*

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Medical Progress

Skeletal Scintigraphy

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Skeletal scintigraphy, using phosphates or diphosphonates labeled with technetium 99m, is a sensitive method of detecting bone abnormalities. The most important and most frequent role of bone scanning is evaluating the skeletal areas in patients who have a primary cancer, especially a malignant condition that has a tendency to spread to bone areas. The bone scan is superior to bone radiographs in diagnosing these abnormalities; 15 percent to 25 percent of patients with breast, prostate or lung cancer, who have normal roentgenograms, also have abnormal scintigrams due to metastases. The majority of bone metastases appear as hot spots on the scan and are easily recognized. The incidence of abnormal bone scans in patients with early stages (I and II) of breast cancer varies from 6 percent to 26 percent, but almost invariably those patients with scan abnormalities have a poor prognosis and should be considered for additional therapies. Progression or regression of bony lesions can be defined through scanning, and abnormal areas can be identified for biopsy. The incidence of metastases in solitary scan lesions in patients with known primary tumors varies from 20 percent to 64 percent. Bone scintigraphy shows positive uptake in 95 percent of cases with acute osteomyelitis. Stress fractures and trauma suspected in battered babies can be diagnosed by scanning before there is radiological evidence. The procedure is free from acute or long-term side effects and, except in cases of very young patients, sedation is seldom necessary.

Although the test is sensitive, it is not specific and therefore it is difficult to overemphasize the importance of clinical, radiographic, biochemical and scanning correlation in each patient.

SKELETAL SCINTIGRAPHY, bone scanning, is one of the most important tests in nuclear medicine. There are two main reasons for this: first, the availability of a variety of bone-seeking phosphate and diphosphonate compounds which can be conveniently and efficiently labeled with technetium 99m; and second, the development of detecting devices which are capable of producing high resolution, whole body images. The benefits of the agents labeled with ^{99m}Tc are that they produce a low radiation dose in patients, their half-lives are convenient for producing images two to four hours after their administration, and the monoenergetic gamma ray (140 keV) is ideal for current imaging devices. Whole body images allow all bones to be evaluated, a task diagnostic radiologists do not undertake with equanimity. Some centers have instruments capable of producing

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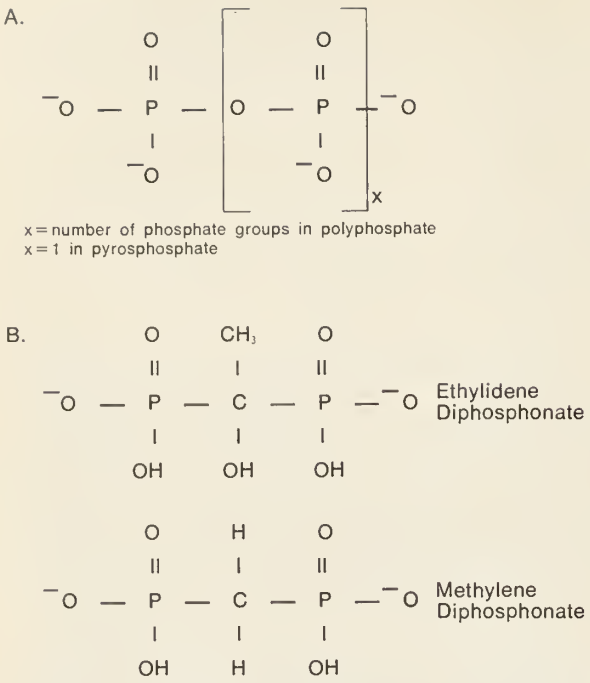

Figure 1.—Structure of phosphates and phosphonates

whole body tomographic images, from which the depth of lesions can be evaluated.

This article will deal with the pharmacology of the bone scanning agents and some important aspects of methodology. The value of bone scanning in patients with cancer will be described, with particular emphasis on breast and prostate cancer. There will follow sections on the use of bone scintigraphy in infectious diseases of the skeleton and in various metabolic bone disorders. A section is devoted to *benign* bone disorders including osteonecrosis and trauma. Nonskeletal disorders seen on bone scan and finally artifacts will be discussed. Joint diseases are not described in this article.

Radiopharmaceutical Agents and Pharmacokinetics

There are several phosphate and phosphonate compounds that can be labeled with ^{99m}Tc. The phosphates include pyrophosphate, polyphosphate[1] and monfluorophosphate.[2] They have the basic structure shown in Figure 1A. Phosphonates include hydroxy-ethylidene diphosphonate[3,4] and methylene diphosphonate; their structure is shown in Figure 1B. All of these compounds are available in commercial kits which can be labeled simply and efficiently *in vitro* with ^{99m}Tc. There are some minor differences in the distribution of these agents after intravenous injection *in vivo*. In general, the phosphonates are cleared from the blood more rapidly by the kidneys and about 60 percent to 70 percent of the material is found in the urine in six hours.[5] The more rapid renal clearance of phosphonates produces a more intense ratio of bone to the background and in some cases a higher ratio of tumor to bone. Therefore, phosphonate scans are easier to interpret. Many investigators agree that the image obtained with diphosphonates is superior to that obtained with phosphates[6] and there is clinical information to suggest that when both agents are compared in the same patient additional lesions are seen in diphosphonate scans.[7,8] Methylene diphosphonate produces a higher ratio of bone to background than ethylidene diphosphonate at all intervals between a half hour to five hours, but it has yet to be shown that additional lesions are detected with this agent.[9,10]

The risk of toxicity from these agents is extremely small in view of the small doses of pharmaceutical agents used[11] and the author is unaware of any clinical or metabolic problems that could be attributed to them.

The phosphate and phosphonates attach to hyroxyapatite crystals through a combination of physical and chemical methods (chemisorption). This leads to the question of increased uptake in abnormal areas such as carcinoma or abscess. The most important factor is blood flow to the bones; increased blood flow to lesions is responsible for increased uptake. A second factor is increased metabolic activity in reactive bone-surrounding lesions, which is less likely because the radiopharmaceutical agent is not primarily in bone cells.

Methods

Bone scans are made about three hours after the intravenous injection of the bone scanning agent. Snow and Weber[12] compared normal and abnormal bone areas with soft tissue in a detailed study using pyrophosphate. They showed that a delay of three to four hours is optimal. In contrast, Potsaid and co-workers[13] believed there was no loss in quality if imaging was conducted at two hours; however, they used diphosphonate. Curtailing the time between injection and scanning to less than two hours is unwise, because the higher background level of radioactivity reduces the quality of the image.

Under certain circumstances there is an advantage in delaying the scan longer than four hours

after injection of the radiopharmaceutical agent.[14] If a proportion of the agent is infiltrated at the time of injection there is a gradual resorption of radioactivity from this site, which causes a higher background, and waiting for six hours frequently produces a better image. If bladder activity makes assessment of the pelvis difficult, even when images are made immediately after micturition, a delay of 24 hours will greatly reduce the bladder contribution.[15] In a study comparing 4-hour and 24-hour bone scans, lesions were enhanced in 13 of 23 patients in the delayed scan: in fact in five patients, abnormalities not seen at four hours became apparent at the later time. The longer the image is delayed, the less radioactivity will be present and the longer the scanning will take.[16]

Each study of a patient has to be evaluated in the context of the clinical problem to be answered. In the majority of patients the scan will be made between two and four hours after injection of the radiopharmaceutical agent.

It is common for spot films to be obtained of areas that appear suspicious on whole body scans. These help determine whether or not a true abnormality is present and are useful in planning biopsy sites and radiotherapy treatment ports. Marking of scan abnormalities for bone biopsy requires meticulous attention and close cooperation between the nuclear physician and the surgeon, who should be present when skin markers, overlying a bony abnormality, are placed.

Under most circumstances, unprocessed bone scans provide all the information the referring physician requires. Several groups of investigators have evaluated quantitation of scans by comparing the uptake of radioactivity in lesions with that in normal bone, or soft tissue.[17-20] This requires the camera to be interfaced with a computer, so that areas of interest can be outlined and count rates within these areas can be measured. A numerical result is obtained from this information and this number can be used for comparison with the numerical result from the same region in subsequent scans. It remains to be seen whether this type of quantitation will provide additional clinically useful information.

In adults, the administered dose of ^{99m}Tc is in the range of 15 to 25 MCi and in children correspondingly lower doses are based on age and weight. Patients of all ages can be evaluated, but in the younger-age groups it may be necessary to have a hypnotic prescribed before attempting the scan. In children it is also wise to inject the radiopharmaceutical agent through an indwelling catheter; this makes the procedure less traumatic for both patient and physician, and also prevents infiltration of the material.

The distribution of a radiopharmaceutical agent is symmetrical in persons without abnormalities. The area with most intense uptake in adults is the axial skeleton. In children it is the metaphyses of long bones. The quality of image deteriorates as the age of the patient increases, and as the thickness of adipose tissue increases. There are variations in normal findings which can only be recognized by reviewing large numbers of scans with knowledge of each patient's history, review of appropriate roentgenograms and subsequent follow-up studies. This article does not dwell on the normal bone scan; Figures 2 and 3, however, show normal scans in an adult and in a child, respectively.

Bone Scanning in Patients With Malignant Disease

Carcinoma of the breast, lung, prostate, kidney and thyroid metastasize to bone areas. The first three are common types of cancer and the occurrence of skeletal metastases significantly alters the prognoses. There are now numerous studies confirming that bone scanning is more sensitive than roentgenograms in evaluating the presence of metastatic lesions.[21-25] In most cases multiple abnormalities of the axial skeleton and ribs, and the pattern of these abnormalities, make the diagnosis of metastasis most likely. Scans are more sensitive than roentgenograms because 50 percent of bone mineral content must be lost before a lesion is radiographically visible,[26] and the scan depends on different factors for positive uptake.

The indications for bone scanning in patients with cancer are: (1) to determine that no metastases are present and (2) to determine the presence of metastases. In ideal circumstances it would be advantageous to have the scan interpreted before surgical operation on the primary lesion is done, because the presence of metastatic lesions might make a major difference in the extent of the procedure. This would be especially true of cancer of the lung, in which the presence of bone metastasis might be considered a reason to cancel surgical treatment. On the other hand, many lesions in the breast are benign and it would be unjustifiable to obtain preoperative scans in all patients in whom breast lumps are to be re-

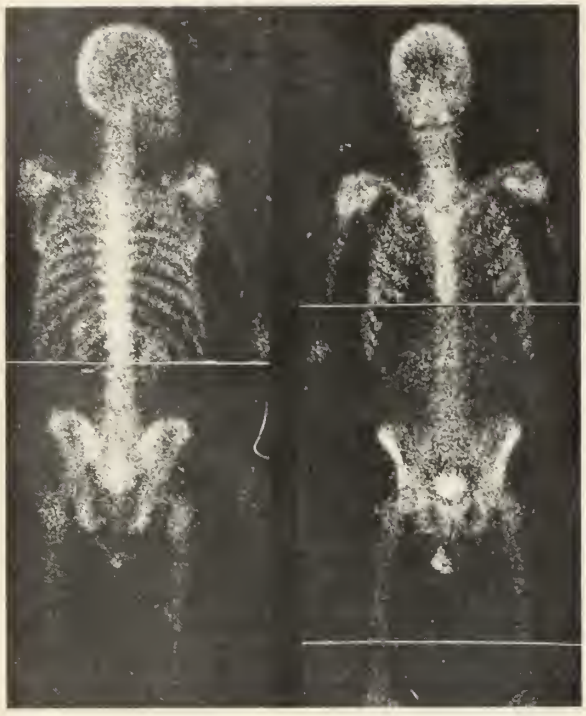

Figure 2.—Anterior and posterior images of the skeleton in a 37-year-old man. Normal distribution of methylene diphosphonate labeled with technetium 99m showing homogeneous symmetrical activity in the axial skeleton.

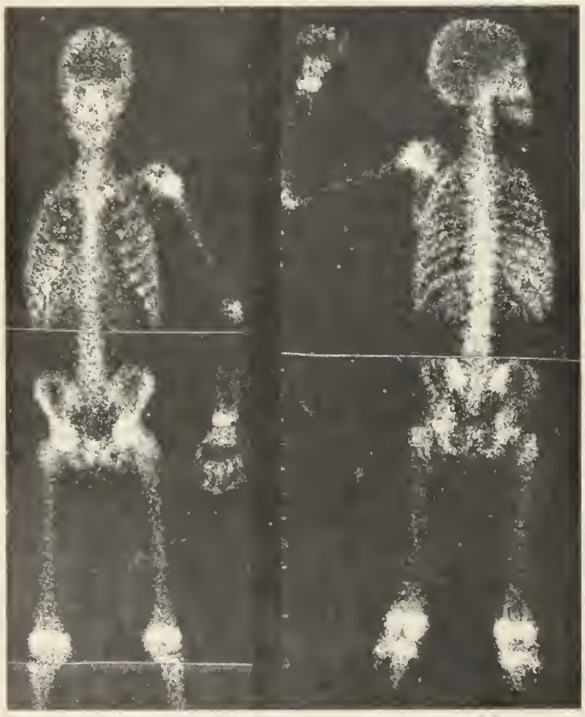

Figure 3.—Posterior and anterior images in a 12-year-old boy who had a right arm disarticulated for treatment of osteogenic sarcoma. The scan is otherwise normal and compared with Figure 1 shows more intense uptake in the growing ends of long bones.

moved. In patients considered most likely to have cancer of the breast, a preoperative scan would be appropriate to (1) define the optimal place for bone biopsy, (2) record progression or regression of disease, (3) provide prognostic information and (4) obtain data about the natural history of cancers with and without bony metastasis.

As far as is possible, from published information, these points will be discussed below.

Breast Cancer

The prevalence of bone metastases on scans from patients with cancer of the breast varies considerably among published reports. It is not possible to explain these differences on the basis of different radiopharmaceutical agents, imaging techniques or detecting equipment. Most likely the differences are related to different patient populations being evaluated.

Campbell and associates[27] found abnormal scans in 26 percent of 80 patients; 18 percent of the abnormal scans were from patients with stage I cancer, and 41 percent in patients with stage II. The site of the breast lesion, or its size, did not correlate with the presence of metastatic lesions; however, there was a high correlation between the presence of these lesions in axillary nodes and an abnormal scan. After 12 months, 54 percent of the patients with abnormal scans had clinical evidence of disseminated disease, compared with 5.7 percent of the patients with normal scans. In a series of 192 patients, abnormal scans were found in only nine patients (5 percent); systemic disease developed in eight (88 percent) of the nine patients and four died. Nine of the 183 patients whose scans were originally normal subsequently had abnormal scans (5 percent).[28] In 50 patients with early cancer of the breast Galasko[29] found bone metastases in 12 (24 percent) who had normal roentgenograms. Disseminated disease developed in all of them and ten patients (83 percent) died within five years. These findings contrasted with the five-year mortality of 34 percent of the patients with normal scans. Citrin and associates[30] conducted a study using sequential scans in 75 patients with stage I or stage II cancer of the breast. Scans from 11 patients (14 percent) showed evidence of metastases and scans from 13 patients changed from normal to abnormal in the course of the study. These patients did poorly whereas only one of 51 patients who had persistently normal scans died. Gerber and coworkers[31] found bone metastases in only 6 percent

Figure 4.—Multiple abnormalities appearing as areas of intense uptake in a patient with metastatic cancer of the prostate.

of 122 patients, but noted a change from normal to abnormal within three months in some patients.

A varying proportion of patients with early primary cancer of the breast (stage I or II) have lesions seen on bone scans (6 percent to 26 percent). A greater percentage of those with advanced cancer of the breast have bone scan findings consistent with metastases. The scan is useful in determining the stages of cancer.[32] Patients with bone metastases, as well as those patients whose bone scan changes from normal to abnormal, have a poor prognosis. It would seem that patients with abnormal scans should be considered for additional therapy, which would be dictated by other factors such as age, menstrual status and estrogen receptor status of the cancer.

Prostate Cancer

Prostate cancer, the most common cancer in men, has a strong tendency to spread to bone areas and the bone scan appearance of metastases in this condition is frequently striking (Figure 4).

In a review of 219 patients, 43 percent of those with proven metastases to the bone and an abnormal scan had no bone pain, 39 percent had normal levels of acid phosphatase and 23 percent had normal values for alkaline phosphatase. In 24 percent of the patients with normal values for enzymes and no clinical evidence of bone disease the scan showed abnormalities which were proved to be metastatic lesions.[33]

Shafer and Reinke[34] carried out studies in 110 patients with cancer of the prostate; 77 had normal bone scans and after two years there was no evidence of skeletal involvement. However, in 18 patients of this group there originally was a rise

Figure 5.—Spot view showing focal uptake of methylene diphosphonate labeled with technetium 99m between ribs on the left side. This was subsequently proven to be metastatic osteogenic sarcoma in the lung.

in levels of alkaline phosphatase and in 12 patients an elevation in levels of acid phosphatase. In the 37 patients with abnormal scans due to metastases, only 25 had abnormal radiograph results, 20 had abnormal alkaline phosphatase levels and 18 had elevated acid phosphatase levels. Pistenma and co-workers[21] found that acid phosphatase did not help differentiate between those patients with and those patients without metastases to the bone.

The bone scan is the most sensitive test for detecting metastatic lesions of the bone in patients with cancer of the prostate and should be part of the evaluation in each patient.

Miscellaneous Tumors

Williams and associates[35] compared skeletal scintigraphy, plain radiographs and serum alkaline phosphatase in 100 patients with cancer of the lung. In this group 56 patients had no evidence of metastases after 18 months follow-up or at the time of death. Bone scans and radiographs were normal in all of these cases. The bone scans were abnormal in 37 of 44 cases in which metastases eventually appeared; and the scans were abnormal in seven cases in which radiographs were normal and there was no bone pain. It is interesting that six of the seven scans giving false-negative findings were in patients with oat-cell carci-

noma. Hypertrophic pulmonary osteoarthropathy appears as increased linear uptake of radioactivity in the edge of long bones, and is most commonly associated with primary cancer of the lung[36,37] but can be found in other diseases.[38]

Hatfield and associates[39] found that only one patient of 16 with pancreatic carcinoma had bone metastasis detected on scan; and in their review of the literature they found autopsy or radiographic evidence of metastases in only 5 percent of 2,155 cases. Similarly Feldman and Plonk[40] found a low incidence of bone metastases in patients with midgut carcinoid tumors. Nevertheless, the 5 percent incidence of bone metastases in patients with carcinoma of the colon and rectum has been reached without bone scans and is most likely an underestimate.[41]

Of 99 patients with urogenital cancer there were abnormal scans in 59; in 52 of the 59 there were abnormal radiographs, but in an additional 11 of the 99 patients the scan showed more extensive involvement than the radiograph.[42]

Osteogenic Sarcoma

Primary bone tumors appear as expansile areas of increased uptake most frequently in the metaphyseal region of long bones such as the tibia and the femur. Metastatic lesions, even those in soft tissues such as lymph nodes and lungs,[43-46] may show active uptake of the bone scanning agents (Figure 5).

Solitary Hot Lesion on Bone Scan

Most bone scans are done to determine the presence of metastatic lesions in patients with known primary cancer. A problem often encountered is the finding of a solitary abnormality in contrast to mutiple lesions. Corcoran and coworkers[47] found this in 171 (15 percent) of 1,129 patients with nonskeletal primary cancer. A definite cause for the scan abnormality was found in 90 cases and 58 cases (64 percent) were due to metastatic disease. In a retrospective study of 861 bone scans, 63 (7.3 percent) showed a solitary lesion; 30 of these 63 were in patients with known primary cancer, and a diagnosis of the scan abnormality was made in 21 of these 30 patients.[48] Only four lesions (20 percent) were metastatic, and the remaining 17 were benign lesions of the bone discovered serendipitously. However, none of these patients had cancer commonly associated with spread to the skeleton, and several patients died of cancer before the causes of the bone scan abnormality could be deter-

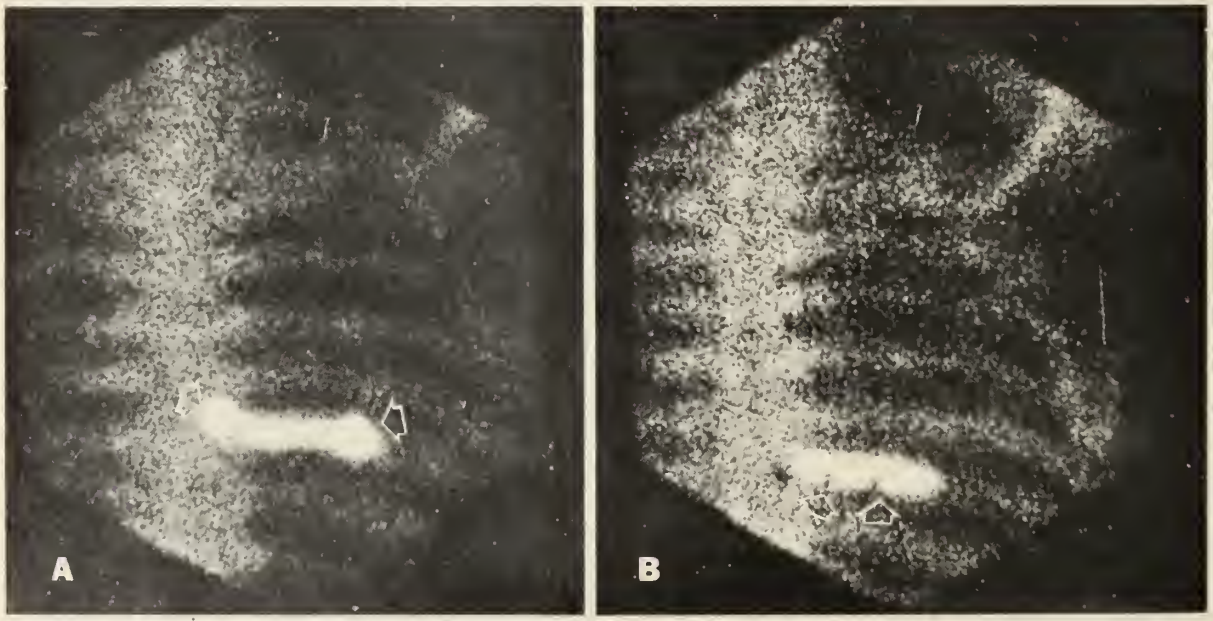

Figure 6.—A rib abnormality which was the solitary lesion on scan in a 57-year-old man with cancer of the prostate. **A**, technetium markers (shown by arrows) were used to position the lesion. Skin marks were then placed in the exact site of the technetium 99m markers as a guide for biopsy. If this technique is employed, great care must be taken to ensure that the patient is in exactly the same position for biopsy as for the scan. **B**, lead markers, which appear as small photopenic areas indicated by arrows, were placed over the abnormal rib. When lesions are marked in this fashion a standard radiograph will then define the exact site of the lesion. Ribs are not easy to count on scan, because the 1st and 12th ribs may be difficult to identify.

Figure 7.—Photon deficient areas in the spine of an 18-month-old child with metastatic neuroblastoma. The primary tumor shows hyperconcentration of the bone scanning agent.

mined. Therefore the 20 percent figure may be somewhat low.

Rather than be discouraged with scans because of the low incidence of malignancy shown in solitary bone lesions (20 percent to 64 percent), clinicians should accept the fact that scans are sensitive but not specific. A false-negative scan, a normal scan with radiological or clinical evidence of cancer, is rare (probably less than 2 percent) but many benign lesions of the bone will be shown and may be difficult to differentiate from metastatic lesions. Frequently, the position of the abnormality (in a joint, for example), the clinical history or a specific radiograph will define the exact nature of a solitary lesion. A single bone scan abnormality with normal radiographic results should be viewed with suspicion for neoplasm, and close clinical, scintigraphic or radiological follow-up studies would be advisable. Figures 6A and 6B show a single rib lesion in a patient with prostate cancer; the x-ray films in this case showed no abnormalities. Prostate cancer was found on a biopsy specimen of the bone. The figure also shows two methods of marking the exact position for biopsy.

Tofe and co-workers,[49] in an analysis of 1,143 whole body scans from various institutes, found single abnormalities in 4 percent of the skulls and 9 percent of the extremities. Half of the skull lesions and 63 percent of the single extremity lesions were found in patients with primary cancer of the breast, lung or prostate. Although the true incidence of cancer in these lesions was not defined, the findings emphasize two facts: first, the importance of obtaining whole body skeletal scintigrams, and second, the need to view with considerable respect any bone scan abnormality in patients with tumors in the breast, lung or prostate.

Abnormalities Appearing as Cold Areas

Most pathologic conditions of bone, such as tumors, infection or trauma, appear more intense than normal bone on a scan because there is a greater concentration of the radiopharmaceutical agent in, or around, the lesion. It is now being recognized with increasing frequency that lesions can also appear less intense. Metastasis,[50-53] sickle cell infarction,[50,52] benign tumors,[54] osteomyelitis and Perthes disease have been described as causes of cold areas. (The last two disorders are discussed more fully in appropriate sections.) Figure 7 shows cold spinal lesions in an infant with metastatic neuroblastoma.

The most probable causes of this finding are (1) the lesions are predominantly osteolytic; (2) the underlying pathologic condition causes reduced blood flow to the area; (3) the specific lesion causes less reactive new bone formation, or (4) any combination of these. Although the finding is uncommon, clinicians should be aware of the possibility and aware that *cold* lesions surrounded by normal bone are harder to see than *hot* lesions.

Summary of Bone Scan in Patients with Malignant Disease

Bone scintigraphy is a highly sensitive test for diagnosing the presence of metastatic lesions of bone, particularly in patients with primary cancer of the breast or prostate. It is useful preoperatively or perioperatively to determine the need for additional therapy and to follow sequentially the stability, progression or regression of disease. The scan has a considerable role in diagnosing cancer of the lung and genitourinary and colorectal areas, and a lesser role in diagnosing cancer of the pancreas. Provided surgical staging with bone marrow biopsy is undertaken in patients with Hodgkin disease and non-Hodgkin lymphoma, the major role of bone scan in these diseases is to

TABLE 1.—*The Ratio of Bone to Soft Tissue Radioactivity in Three Disorders*

Patients Studied	*Ratio of bone/soft tissue radioactivity at 4 hours*
Normal	4.05 (±0.69)
Primary hyperparathyroidism	3.76 (±0.26)
Renal osteodystrophy	6.29 (±1.6)
Osteomalacia	6.06 (±1.85)

detect patients in whom there are relapses localized in the bone or marrow.

Metabolic Bone Diseases

This section deals with primary hyperparathyroidism, osteomalacia and renal osteodystrophy (secondary hyperparathyroidism). Frequently bone scans show a characteristic pattern, especially in osteomalacia.[55] The characteristic features, which may not all be present in one patient, are a subjective impression of increased bone uptake of tracer, beading of the costochondral junction, increased activity in the calvarium and mandible, faint renal images and prominent (tie) sternum and pseudofractures. These findings have been described individually, or in combination, by other investigators.[56-58]

Investigators have analyzed the information by measuring plasma radioactivity (at specific times after injection of the bone scanning material), whole body retention, urinary outputs, and ratio of bone to soft tissue radioactivity. Using the data from Fogelman and co-workers,[59] the ratio of bone to soft tissue radioactivity in different disorders is shown in Table 1. The results in cases of primary hyperparathyroidism are not different from normal findings, and although patients with osteomalacia and renal osteodystrophy have a higher ratio of bone to soft tissue radioactivity than do patients without the diseases, there is considerable overlap.

Krishnamurthy and associates[60] carried out studies in 12 patients with hyperparathyroidism by using bone scans, blood clearance of the radiopharmaceutical agent, urinary excretion of the radiopharmaceutical agent and standard radiographs. In seven of the 12 patients there were abnormal scans. These investigators could not differentiate, on the basis of blood clearance, between patients with primary hyperparathyroidism and patients without disease. Wiegmann and associates[61] found that 11 of 20 patients with primary hyperparathyroidism had normal bone to soft tissue ratios, whereas five patients with secondary hyperparathyroidism could be differentiated from persons without disease.

In summary, in patients with well established metabolic bone disease the scan may show a characteristic pattern which should not be confused with that of metastatic disease. Earlier cases may not be easy to recognize and additional tests on blood and urine to determine the rate of clearance of the radiopharmaceutical agent might be helpful in osteomalacia and secondary hyperparathyroidism. This is not the case in primary hyperparathyroidism, which may be difficult to diagnose on the basis of radionuclide studies.

Paget Disease

In Paget disease of the skeleton, bone scans frequently have a characteristic appearance.[62,63] Entire bones such as the femur, tibia and ilium appear thicker and show intense uptake of the radiopharmaceutical agent. This is most likely due to increased flow of blood to diseased bones.

In mild cases, biochemical results including alkaline phosphatase and urinary hydroxyproline may be normal, though the bone scan clearly delineates abnormal areas.[64] Moderately severe cases can be diagnosed clinically, biochemically and by scanning. It was hoped that serial scans or analysis of the bone scan, including evaluation of blood clearance and urinary excretion of the radiopharmaceutical agent, would provide an accurate method of evaluating the response of the disease to therapy (such as with thyrocalcitonin). This is the case in patients with a mild form of the disease, but not in moderate or severe cases.[64]

Osteomyelitis

Early diagnosis of osteomyelitis is important so that destruction of bone and septic metastasis can be prevented. Radiographic changes may not occur for ten days to several weeks after the onset of the disease, and any test that directs physicians' attention to an abnormal site at an earlier time is a great advantage. Bone scintigraphy is a sensitive method of detecting osteomyelitis by showing increased uptake of radiopharmaceutical agents in the region of bone abscess.

Duszynski and co-workers,[65] using bone scans, diagnosed the disease correctly in 18 of 19 patients who subsequently were shown to have osteomyelitis. In only one case in this group were the abnormalities not shown on a radiograph. In another series of 19 patients with proven osteo-

Figure 8.—Anterior view of head and torso in a patient with Hodgkin disease which shows intense uptake in maxilla and mandible resulting from a severe dental disease with apical abscesses.

myelitis, the bone scans showed the abnormal sites in 16 cases. In ten of the 16 cases roentgenograms showed no abnormalities.[66] Kempi and van der Linden[67] found scans to be positive in all of 14 cases in which patients were thought to have osteomyelitis; in seven cases the roentgenograms showed abnormalities at the time of scanning, and in the remainder there were abnormal findings on roentgenograms 1 to 20 weeks after the scintigrams were done. Osteomyelitis found in unusual sites such as the mandible[68,69] or sacroiliac regions[70] can be detected. Figure 8 shows the scan appearance of apical dental disease. Handmaker and Leonards[71] showed that the scan may be abnormal within 24 hours of the appearance of symptoms; however, this raises an important question regarding the meaning of normal scan results in cases of suspected osteomyelitis. In most series there is a small number of patients in whom the scan does not show abnormal uptake; in two studies discussed above, this occurred in one of 19 patients[65] and in three of 19 patients.[66] Indeed, there are reports of cases in which osteomyelitis appears as a cold area.[72-75] Clinicians should be aware of the fact that osteomyelitis does not always appear as a hot area. Most likely in the early phase of osteomyelitis, acute inflammation of the bone and marrow causes thrombosis of arterioles and capillaries, and reduces the blood flow to the area. With reduced blood flow, a reduced amount of the radiopharmaceutical agent is deposited, and a normal or cold area appears on the scan. A model of osteomyelitis in rabbits showed similar findings.[76] What should be done in the small number of patients in whom osteomyelitis is suspected, when scans and radiographs are normal? Probably the best

Figure 9.—Spot view of hip joints in an 8-year-old showing Perthes disease.

approach is to use a gallium 67 scan; results are almost always abnormal in these circumstances. Because the bone scan is usually abnormal and because of the higher radiation dose and poorer resolution of ^{67}Ga, it is unnecessary to use ^{67}Ga scans in all cases. ^{67}Ga scans are preferable to conventional bone scintigraphy for determining whether or not the infection has resolved, because the bone scan may remain abnormal for weeks or months. In most patients, careful clinical judgment and evaluation of leukocyte counts and differentials, and the erythrocyte sedimentation rate, may be more satisfactory in determining resolution—and they are less expensive. An alternative, but not yet fully evaluated approach, would be to use autologous leukocytes labeled with indium 111.

Uncommon chronic forms of osteomyelitis, such as tuberculosis[77] and leprosy,[78] may be noted on scans as areas of increased uptake of radiopharmaceutical agents. Scans also have been found useful in diagnosing osteomyelitis in drug abusers.[79]

Bone scintigraphy is a sensitive method of detecting osteomyelitis. Whether or not earlier diagnosis of the disease will result in a shorter period of treatment remains to be seen.

Benign and Traumatic Abnormalities

Osteonecrosis

There have been considerable data supporting the fact that bone scans are superior to standard radiographs for the early detection of osteonecrosis. If the scan is conducted at a very early stage in the evolution of the osteonecrosis, a cold avascular area will be seen. This is more frequently encountered in patients with Perthes disease than in those with steroid-induced osteonecrosis.[80] It is more likely that the scan will show

increased uptake of radiopharmaceutical agents around the affected area, probably as a result of reactive bone formation.[81,82] Figure 9 shows an avascular hip in a patient with Perthes disease.

Trauma

Most cases of bone trauma are best evaluated with roentgenography; however, stress fractures are frequently not recognized on radiography until the healing phase occurs. If it is important to record the presence of a fracture—such as in troops or athletes—a bone scan is a sensitive method of showing the lesion.[83,84] Bone scans are also valuable in diagnosing and showing the extent of trauma in battered babies.[85]

Nonskeletal Abnormalities Seen on Bone Scan

A large number of nonskeletal abnormalities, both malignant and benign, concentrate bone-seeking radiopharmaceutical agents. The most important is acute myocardial infarction, and pyrophosphate labeled with technetium 99m is used commonly as an aid in making this diagnosis.[86,87] Cerebral infarct[88] and cerebral tumors[89] show positive uptake as do a spectrum of hepatic disorders including metastatic lesions of the colon,[90] amyloidosis,[91] and hepatic necrosis.[92] Primary cancer of the breast[93] and a normal breast[94] can occasionally show increased concentration This list is not complete and readers are referred to the reviews by Fratkin[92] and Oren and Uszler.[95]

Renal Findings on Bone Scan

Of bone scanning agents, 50 percent to 60 percent are cleared by the kidneys and excreted in the urine; as a result, it is not unusual for renal or bladder lesions to be detected. Therefore, it is important for these structures to be carefully evaluated when a bone scan is read.

In an analysis of 1,711 bone scans, renal abnormalities were found in 247.[96] In all, 52 were graded as significant and included polycystic disease and renal cell carcinoma. Hydronephrosis, hydroureter, cysts, carcinoma and nonfunctioning kidney were among nine abnormalities found in 52 patients.[97] Vieras and Boyd[98] found that only one of 751 normal-appearing kidneys on bone scan had a radiographic renal abnormality, and when the radionuclide image was abnormal the result was confirmed radiographically in 84 percent of patients. Unexpected renal findings have also been described by Mandel and associates[99]

Figure 10.—Intense uptake of bone-seeking radiopharmaceutical agent in the kidneys of a child who had received antitumor chemotherapy.

and rare renal malformations, such as horseshoe kidney, have been encountered.

Renal carcinoma usually apears as a filling defect on the scan[100] but there are reports of cases in which there is increased uptake in the tumor,[101,102] a finding that has not been adequately explained.

Lutrin and co-workers[103] have described intense uptake of bone scanning agents in the kidneys of children receiving antitumor chemotherapy (Figure 10). This association was noted in children who had received cyclophosphamide, doxorubicin hydrochloride and vincristine. The cause of this finding has not been defined, but it is probably related to direct toxicity of the antitumor drugs in renal tubular cells.

Artifacts on Bone Scintigram

One half of the x-rays emitted by technetium 99m are attenuated by 5 cm of tissue. Denser materials overlying the patient such as a silicone breast prosthesis, belt buckle, hip flask or pacemaker may conceal bones and pathologic conditions may be overlooked.[104] Occasionally barium in the bowel[105] or even a large meal[106] can cause a photopenic area. Contamination with urine containing radioactivity may produce a false positive lesion. The nuclear specalist should be responsible for evaluating each scan before the patient is discharged from the department. It may be necessary to correlate clinical information, review past history of trauma, obtain spot views of abnormal areas and even to do some detective work to explain each abnormality on the scan.

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Specialty Conference

Moderator
JOHN E. EDWARDS, Jr., MD

Discussants
DAVID B. TILLMAN, MD
MICHAEL E. MILLER, MD
HOWARD E. PITCHON, MD

This is an edited transcript of one of the regular teaching conferences in Infectious Diseases held weekly at Harbor-UCLA Medical Center, Torrance, CA. This transcript has been edited by John E. Edwards, Jr., MD, and Lucien B. Guze, MD

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Infection and Diabetes Mellitus

JOHN E. EDWARDS, JR., MD:* *Advances of recent years have elucidated several of the causes of the suboptimal response to infection in diabetic persons, although much remains to be learned. While granulocyte dysfunction has been the focus of most recent investigation, work has also begun in the area of lymphocyte function. Despite a substantial literature on the association of infection and diabetes mellitus—most of which is approximately 15 years old—it remains unsubstantiated that there actually is a generalized increase in the frequency of infections. What does appear clear, however, especially when recent immunological discoveries related to diabetes mellitus are taken into consideration, is "When infections do occur in diabetic patients, they tend to be protracted and severe."*[1]

The purpose of this conference is to discuss the association of infection with diabetes mellitus and to review the current concepts of the pathophysiology of infection in this disease. We will begin with Dr. David Tillman's review of the types of infection associated with the disease and the nonimmune mechanisms which may be responsible for their pathogenesis.

DAVID B. TILLMAN, MD:† This portion of the conference concentrates on three aspects of infection in diabetic persons: First, the clinical studies questioning the assumption that infection occurs more frequently in persons with the disease will be examined. Second, the nonimmunologic factors that may account for an increased rate of certain types of infections will be discussed. Third, some types of infections that are classically associated with the disease will be enumerated and described.

Do Infections Occur More Often?

A common assumption held by many clinicians is that diabetic patients have a generalized increase in susceptibility to infection compared with nondiabetic patients. However, the available data fail to support this hypothesis for most types of infection. In an autopsy analysis of more than 300 persons with the disease compared with 2,800 nondiabetic patients, the causes of death and the incidence of pulmonary and most other infections

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were not significantly different. A greater incidence of pyelonephritis and infections of the extremities in the persons with the disease was documented.[2] Pell and D'Alonzo[3] followed the cases of a large group of diabetic patients and controls for ten years; infection was not an important cause of death in either group. Cohen and co-workers,[4] in a study of 143 cases of postoperative staphylococcal wound infections, could not correlate diabetes mellitus with an increased risk of infection.

Although the frequency of most infections may not be increased, the morbidity of infection may be of greater magnitude. A study of 662 diabetic employees of the DuPont Company showed that the number of infectious illnesses causing absence from work was not statistically different from age-matched and job-matched nondiabetic controls. Prolonged disability was more common among the diabetic subjects, however. Disability of ten or more days was seen in 27.7 percent of those with the disease and in only 14.8 percent of controls ($p<0.01$).[5]

Nonimmunologic Factors

The specific effects of diabetes on the immune system will be discussed by Drs. Miller and Pitchon. Clearly, however, the vascular disease, the neuropathy and the hyperglycemia associated with diabetes mellitus can cause certain infections to be both more frequent and more severe. The peripheral vascular disease, common in advanced diabetes, undoubtedly increases the risk for infection. Vejlsgaard[6] found a pronounced correlation between the incidence of urinary tract infections and the presence of generalized vascular disease in persons with diabetes. The correlation was independent of duration of disease, the presence of neurogenic bladder or nephropathy. Since the normal response to infection involves increased local circulation, the host response to infection, occurring in an extremity where vascular supply is compromised, is adversely modified.

Neuropathy predisposes both diabetic and nondiabetic patients to infection. The neurogenic bladder with residual urine allows for multiplication of organisms within the bladder. Bladder dysfunction is present even in many asymptomatic cases of diabetes mellitus.[7] Urinary retention may also lead to instrumentation of the bladder, which results in iatrogenic infection. In addition, the sensory deficit of the extremities may cause a patient to ignore minor trauma and allow development of a significant infection.

Hyperglycemia itself may influence the growth of microorganisms, but even this observation has not been well documented. Robson and Heggers,[8] using plasma with varying amounts of added glucose, noted that Gram-positive organisms thrived on high sugar levels while Gram-negatives grew poorly. In experimental studies in rabbits and mice, there has been little difference noted in the extent of induced infection in animals made hyperglycemic by intravenous infusion of glucose as compared with controls.[9] Other metabolic changes seen in diabetic patients may alter the growth of certain organisms. These abnormalities will be included in the following discussion of tuberculosis.

Specific Infections Associated With Diabetes Mellitus

Urinary Tract Infections

As noted above, urinary tract infection is more likely to develop in cases of diabetes mellitus in which there is severe vascular disease or neuropathy. Persons with well-controlled diabetes and young persons with the disease seem to have the same incidence of urinary tract infection as age-matched nondiabetic controls.[10,11] It is only after the complications of diabetes (particularly neurological and vascular) have occurred that the incidence of urinary tract infection increases significantly.

On the other hand, pyelonephritis may be seen more often among diabetic patients. Autopsy series have shown histologic evidence for pyelonephritis in as many as 20 percent.[12-14] Robbins and Tucker[2] found acute pyelonephritis at autopsy in 6.8 percent of diabetic and 1.6 percent of nondiabetic subjects. A possible explanation for this increased rate may be reflected in the studies that show obstruction of the lower urinary tract in experimental animals enhances the development of pyelonephritis. The neurogenic bladder by its obstruction of normal urine flow may have the same effect. There are no controlled studies which compare the frequency of *clinical* pyelonephritis in diabetic and nondiabetic patients. In recent years, the relationship between chronic renal parenchymal infection and the histologic diagnosis of pyelonephritis has been questioned. That is, the pathologic diagnosis may not signify chronic infection in these patients and may represent a disease modified by noninfectious factors. There-

fore, it remains uncertain whether pyelonephritis caused by acute persistent infection by a microorganism occurs more often in diabetic than in nondiabetic persons.

Other diseases of the urinary tract that occur with greater frequency in diabetes mellitus and that also may have associated infection are renal papillary necrosis[17] and cystitis emphysematosa.[18] The presence of small vessel disease superimposed on renal parenchymal infection may account for the high incidence of renal papillary necrosis in diabetic persons. Cystitis emphysematosa is characterized by the presence of gas vesicles in the bladder wall. It is associated with infection by coliform organisms in patients with glycosuria. A history of pneumoturia may be obtained although the diagnosis is made radiographically. Its course is benign.

Tuberculosis

The American Thoracic Society includes patients with diabetes in their list of patients who are considered immunosuppressed enough to require isoniazid for a positive PPD (purified protein derivative).[19] If diabetic persons are more susceptible to acquiring active tuberculosis than the general population, then one would expect to find an increased incidence of diabetes within a group of patients with tuberculosis. Mullen and Higgens[20] found diabetes in 4.2 percent of 118 adult patients in a tuberculosis sanitarium. This figure compares to an incidence of 2.9 percent of diabetes among adults in a nearby geographic region. Similar studies have not shown a difference between these two groups. However, the clinical course of this infection seems to follow a different pattern in diabetics. *Diabetic tuberculosis* has been described as an acute, exudative, rapidly caseating disease that progresses to a toxic downhill course.[21] Patients with diabetes also present with more advanced disease and have more lower lobe disease.[22] Because of the multiple drug therapy now available, this acute form of tuberculosis can usually be treated effectively. The death rate from tuberculosis among diabetic persons has fallen from 5.5 percent in the 1920's to 0.3 percent in the 1960's. However, this rate is still higher than in the general population.

What is it about diabetes that seems to make the development of active tuberculosis more likely and makes the disease behave differently? Drs. Miller and Pitchon will discuss cellular and humoral deficiencies which may explain the course and frequency of tuberculosis in diabetes mellitus. It should be noted that other factors may also play a role. For instance, increased levels of glycerol from the metabolism of fat may be important. Glycerol is known to enhance the growth of tubercle bacilli and is included in the culture medium for mycobacteria. Forced feedings of glycerol to rats increased their susceptibility to tuberculosis.[23] In addition, Dubos[24] showed, in 1953, that the growth of both mycobacteria and staphylococci is enhanced by adding dihydroxyacetone or beta-hydroxybutyric acid to their environment. This study was carried out using an already acidic medium to approximate the conditions encountered by these organisms in inflammatory areas and in the intracellular environment of leukocytes after phagocytosis.

Fungal Infections

Mucocutaneous candidiasis is a relatively frequent problem in diabetic patients. It occurs especially in the diabetic women in whom pruritis vulvae may follow a period of glycosuria. Knight and Fletcher[25] have shown a direct correlation between the concentration of glucose in saliva and the *in vitro* growth of Candida species. This correlation may explain the increased frequency of mucocutaneous Candida infections in cases of poorly controlled diabetes. These infections usually resolve with local care once the glycosuria has been treated.

Intertrigo, especially with infection by Candida organisms, is associated with diabetes in the minds of many physicians. Although it may be difficult to eradicate in cases of poorly controlled disease, there is no evidence that this infection occurs more frequently in persons with diabetes than in others.

Mucormycosis is a rare, extremely difficult to treat and often fatal disease associated with diabetic ketoacidosis. The ubiquitous organisms invade through nasal passages producing black necrotic tissue and black pus. Cerebral involvement which occurs in about two thirds of infections can produce proptosis, ophthalmoplegia, headache and signs of diffuse cerebrovascular involvement. Treatment consists of correction of the acidosis, administration of amphotericin B and surgical drainage when possible, but the disease is usually fatal. Sheldon and Bauer[9,26] in experimental infections in animals showed that acidosis, not hyperglycemia, causes the defect in host response that leads to clinical infection. They

showed diminished polymorphonuclear migration and increased growth of fungus in rabbits with acute alloxan diabetes. Rabbits made hyperglycemic by an infusion of glucose resembled nondiabetic controls in their response to fungal infection. Therefore, both clinical and laboratory observation of this disease underline the importance of controlling the patient's metabolic problems in preventing and treating mucormycosis.

Soft Tissue Infections

Infections of the skin and extremities. It has been accepted that staphylococcal infections of the skin occur frequently in persons with diabetes mellitus. Supporting this assumption is the observation that when compared with persons who do not have the disease and persons with the disease receiving oral hypoglycemics, the insulin-using diabetic patients have a higher carrier rate of Staphylococcus aureus on their skin and mucous membranes.[27,28] These same insulin-using diabetic persons also violate their skin each day. When studied clinically, however, this conjecture proves untrue. For example, diabetes mellitus has been observed only rarely among patients with recurrent furunculosis.[29]

Nonclostridial Gas Gangrene

An infection seen commonly in diabetic patients is nonclostridial gas gangrene. Bessman and Wagner[30] reported in 1975 on their experience with 278 admissions of diabetic patients with orthopedic vascular problems. Of these 17 percent (48 patients) had nonclostridial gas containing infections and only 0.3 percent (one patient) had clostridial gangrene. Those with nonclostridial gas gangrene had polymicrobial infections with Gram-negative rods and enterococci. Since extensive surgical treatment, usually above the knee amputation, is recommended for clostridial gangrene, it is extremely important to make the specific diagnosis of nonclostridial gas gangrene. Bessman and Wagner noted that 41 of their 48 patients with nonclostridial gas gangrene received below-knee or more distal amputations. In only one patient was above-knee amputation required. The choice of antibiotics would be different from the penicillin one would choose for a clostridial infection.

Osteomyelitis

Osteomyelitis is another infection frequently associated with diabetes. This infection is undoubtedly secondary to the neuropathy and vascular disease accompanying diabetes. Of 415 cases of osteomyelitis seen at the Joslin Clinic over seven years, 408 occurred in an extremity and all but one were due to extension from a local infection.[31]

Malignant Pseudomonas External Otitis

Malignant external otitis is an uncommon infection usually seen in elderly persons; all but a handful of the reported cases have been in persons with diabetes.[32] It is a severe, necrotizing external auditory canal infection with high morbidity and mortality. The infection begins insidiously, but it is characterized by a gradually worsening, painful, purulent discharge associated with a polypoid mass of granulation tissue. Without prompt recognition and therapy, the mortality may approach 40 percent. Therapy should include debridement, use of a gentamicin wick, and systemic administration of gentamicin and carbenicillin. The reasons for the preponderance of this infection in those with diabetes mellitus is not clear.

MICHAEL E. MILLER, MD:* Current data have suggested that a basic defect in cell movement contributes to impaired host defenses in diabetes mellitus. In this discussion, we will summarize the studies leading to this impression and cite recent evidence that offers a new interpretation.

In 1966 Drachman and co-workers[33] studied chronically diabetic rats and concluded that both *in vivo* and *in vitro* phagocytic capabilities of polymorphonuclear leukocytes (PMN) were adversely affected by high levels of glucose. They suggested that such phenomena, not observed by other workers, could only be shown under conditions that (1) stimulate the cellular crowding of full-grown inflammatory exudates and (2) extend the phagocytic capabilities of the cells. The status of these studies is still in doubt. A number of equally critical and sensitive phagocytic systems have failed to provide similar data. It is possible that the data obtained by Drachman and coworkers reflected a chemotactic deficiency similar to those now to be described.

Three different groups of investigators have reported abnormal chemotaxis in adults[34] and children[35,36] with diabetes mellitus. In our studies,[35] defective response was observed either with (1) PMN's from children with diabetes mellitus or (2) generation of chemotactically active materials

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from plasma or serum of diabetic children. We presently have no explanation for the deficiency in generation of humoral chemotactic activity.

Further investigations have shown an apparent stimulatory effect of insulin upon diabetic PMN chemotaxis.[34-36] Although PMN chemotaxis improved upon addition of insulin *in vitro,* no relationship between insulin levels *in vivo* and degree of PMN chemotaxis has been shown to exist.

Further evidence of defective PMN function in diabetes mellitus has come from three recent reports: (1) Using the technique of cell elastimetry,[37] Miller and Myers have found diminished membrane deformability of PMN's from insulin-treated juvenile diabetes.[38] PMN's were, in other words, more rigid than normal. (2) Bagdade and Steward have shown impaired adherence of PMN's from poorly controlled diabetic patients. (3) Marigo and Bersezio[40] have found reduced osmotic resistance in PMN's from juvenile onset, insulin-dependent diabetic patients, which did not correlate with the duration of diabetes or blood glucose levels.

In a provocative study, Humbert and co-workers[41] suggested that decreased adhesiveness of diabetic PMN's is responsible for the apparent *in vitro* chemotactic defect observed.[34-36] Further work will be necessary to clarify this point.

Finally, very recent data suggest that PMN function in diabetes mellitus may be entirely normal *before* the institution of insulin therapy. In eight children with juvenile diabetes,[42] no defect in PMN movement could be shown before insulin therapy. Following insulin administration, sometimes within 12 to 24 hours, highly significant decreases were found in both cellular and humoral chemotaxis. The significance of this finding remains to be determined.

In summary, much controversy surrounds the question of host defense mechanisms in diabetes mellitus. The nature of specific defects, their relationship to insulin and their *in vivo* significance continue to provide compelling research questions.

Cellular Immunity in Diabetes Mellitus

HOWARD E. PITCHON, MD:* With respect to humoral immunity, it has been shown that normal levels of complement are present as well as normal antibody response.[43-45] In addition, normal circulating numbers and percentages of B-cells have been shown.[46]

With regard to cell-mediated or T-cell mediated immune response in diabetes, there have been a limited number of investigations over the past several years. Animal models of disseminated candidiasis have shown an increased susceptibility to disseminated Candida infection in diabetic animals, implicating a possible derangement of T-cell function with diabetes mellitus or hyperglycemia.[47] An early study[48] of lymphocytes of diabetic patients showed depressed glucose metabolism of lymphocytes; several patients had an associated decrease of lymphocyte transformation to phytohemagglutinin (PHA); however, they were all under poor control. Ragab, Hazlett and Cowan[49] found no difference in lymphocyte transformation to PHA in patients with well-controlled diabetes when compared with normal subjects.

Subsequent studies by MacCuish and co-workers[46] showed that lymphocyte transformation to PHA in persons with diabetes mellitus was related to the control of hyperglycemia. With good control no consistent defect in PHA transformation could be shown; however, with poor control (fasting glucose greater than 350 mg per dl or ketosis) there was significant depression of lymphocyte transformation to PHA. Furthermore, they have also shown that this depressed PHA response in patients with poorly-controlled disease improved with correction of the metabolic abnormalities.[46,50,51] Additional experiments have shown that high glucose concentrations *in vitro* (300 mg per dl to 600 mg per dl of culture medium) and high concentrations of free fatty acids *in vitro* significantly depress PHA transformation of normal lymphocytes.[51] Also, they found no change from normal in the number or percentage of circulating T-cells in diabetic persons whether well or poorly controlled. Therefore, they have concluded that the depressed mitogenic response to PHA in diabetic persons reflects poor metabolic control rather than a genetically determined, inherent abnormality of the lymphocyte.

Delespesse and co-workers[52] found depressed PHA-induced lymphocyte transformation in all the diabetic patients tested regardless of how well-controlled the disease was. However, further analysis of their data showed that the patients who had the poorest metabolic control also had the most depressed PHA reactivity of their lymphocyte cultures. Consequently, they concluded that the

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lymphocyte abnormality was due to both an inherent genetic defect and metabolic disturbance.[52,53]

On the basis of the above studies, lymphocyte transformation to PHA is related to the control of the patients' diabetes. With good control, no consistent defect in PHA transformation can be shown. With poor control resulting in significant hyperglycemia or ketosis (or both) there is significant depression of PHA-induced lymphocyte transformation. Whether there is an inherent genetic defect of the lymphocyte in addition to the metabolic defect is presently an unanswered question.

Other studies of diabetes mellitus have shown no abnormalities of transformation of lymphocytes to specific antigens[49] or mixed lymphocyte cultures.[52] A recent study using mice in which diabetes was induced with alloxan and streptozotocin has shown decreased dermal reactivity and allograft rejection when the disease was poorly controlled in the animals.[54] However, treatment with insulin corrected these abnormalities.

In conclusion, no consistent defect in cell-mediated immunity has been shown in diabetes mellitus that would implicate an inherent genetic defect. When the state of poor diabetic control exists, it can be shown that there is altered lymphocyte glucose metabolism and this abnormality may be related to the altered lymphocyte function seen with lymphocytes from patients with poor control. Possibly with the increasing sophistication taking place in immunology, further defects that are more subtle to detect will be found in lymphocyte subpopulations from diabetic patients.

Summary

DR. EDWARDS: *The available data indicate that persons with diabetes do not necessarily have an increased incidence of infections in general. However, a group of infections do occur with increased frequency in these persons. Included in this group of infections are soft tissue infections of the extremities, osteomyelitis, urinary tract infections and pyelonephritis (especially in older persons with diabetes mellitus), mucocutaneous candidiasis, nonclostridial gas gangrene, mucormycosis, tuberculosis and malignant pseudomonas external otitis.*

Although there is considerable controversy regarding the nature of specific immune defects in diabetes, their relationship to insulin and their in vivo *significance, current data suggest that there is a defect in chemotaxis of polymorphonuclear leukocytes in diabetic patients. This defect may be in the cells themselves or in the generation of chemotactically active materials from plasma or serum. Of particular interest is the provocative observation that children with juvenile diabetes do not have abnormalities of leukocyte movement until after insulin therapy is begun.*

Studies of T-cell mediated immune response in those with the disease are limited and their results are controversial, but they suggest decreased responses of lymphocyte to mitogenic stimuli which are correlated with poor control and metabolic abnormalities rather than inherent abnormalities of the lymphocyte.

It is hoped that further elucidation of the mechanisms responsibile for the select group of infections that do occur with increased frequency in association with diabetes mellitus may lead to prevention and optimal management.

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Specialty Conference

Moderator

EUGENE D. ROBIN, MD

Participants

FUAD ABUABARA, BS
EUGENE D. ROBIN, MD
CHRISTOPHER MYERS, MD
JAMES THEODORE, MD
PATRICK HAMNER, MD
THOMAS RAFFIN, MD
ALLAN HANCE, MD
ANDREW NEWMAN, MD
PATRICIA LYNNE-DAVIES, MD

From Pulmonary Rounds at Stanford University School of Medicine. This has been edited by Doctors Andrew Newman, Norman J. Lewiston and Eugene D. Robin.

Refer to: Robin ED, Abuabara F, Myers C, et al: Pectus excavatum and cardiopulmonary complications—Stanford University School of Medicine Pulmonary Rounds (Specialty Conference). West J Med 130:522-530, Jun 1979

Pectus Excavatum and Cardiopulmonary Complications

FUAD ABUABARA:† The case for discussion this morning is that of a 64-year-old woman admitted to the cardiology service for evaluation of pericardial effusion, atrial fibrillation and mitral regurgitation. The cardiologists were perplexed by her extreme dyspnea on exertion and asked us to evaluate her case for possible pulmonary disease.

The patient considered herself well until 1967, when there was an episode of paroxysmal atrial fibrillation (PAF) which was successfully treated with digoxin. There were similar episodes of PAF in 1968, 1969 and 1974. These were treated with digoxin and either propranolol or quinidine. Since 1974 there have been short episodes of palpitations and light headedness at least weekly.

In January 1977 the patient was seen in Letterman Army Medical Center, San Francisco, with PAF. An echocardiogram indicated mitral valve prolapse. An electrocardiogram showed a 2-mm ST segment depression in the precordial leads. There was no evidence of shunt on a technetium Tc 99m shunt study. On August 10, 1977, the patient was seen at Stanford University Hospital with shortness of breath, fatigue, indigestion and a 9-pound weight loss over three months. The diagnosis was atrial fibrillation and mitral regurgitation. She was treated initially with propranolol as an outpatient, and then with intermittent oxygen for extreme dyspnea. This was unsuccessful in relieving symptoms and she was admitted to hospital for examination.

As a child she had had scarlet fever and Sydenham chorea (St. Vitus' dance). Subsequently a heart murmur developed and she was told to restrict her activities. She had a successful pregnancy without cardiac complications and obtained health insurance without difficulty. Moderate scoliosis and severe pectus excavatum were noted in childhood. She had had a tonsillectomy as a child. Saphenous vein stripping was done in 1959 and a benign right ovarian tumor was removed in 1967.

On physical examination, the patient was found to be pleasant and in no distress at rest. The pulse

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rate was 78 per minute and regular. Blood pressure was 115/80 mm of mercury. The respiratory rate was 16 per minute. Findings on chest examination were a pronounced pectus excavatum and scoliosis of the thoracic spine with concavity to the left. Excursion of the chest wall was moderately restricted. A systolic murmur consistent with mitral regurgitation was noted intermittently.

Cardiac catheterization showed mitral valve prolapse. The left ventricular end diastolic pressure increased from 10 torr to 28 torr with exercise. Pulmonary artery wedge pressure rose from a mean of 10 to a mean of 18 torr with elevation of the legs. There was no cardiac shunt shown by hydrogen inhalation study. A sector scan showed a minimal apical pericardial effusion. Pulmonary angiography and coronary ateriography were normal. Pulmonary function tests showed mild obstructive disease.

Results of exercise studies showed the bicarbonate value decreased from 27 to 21 mEq per liter with mild exercise while arterial oxygen pressure (Pao_2) remained at 97 torr and arterial carbon dioxide pressure ($Paco_2$) remained at 35 torr. These studies suggested that circulatory factors limited the degree of exercise.

EUGENE D. ROBIN, MD:* *The patient had mitral regurgitation. Do you wish to speculate on the origin of that?*

MR. ABUABARA: She had had scarlet fever and St. Vitus' dance, both manifestations of streptococcal infection, and a murmur developed later. She was told to restrict her activities. Mitral regurgitation can result from rheumatic fever with carditis. I suppose it could also be congenital.

DR. ROBIN: *It is conceivable, therefore, that she had three abnormalities, all congenital in origin. What you would want to know, I suppose, would be the temporal relationships between the development of the spine and when scoliosis can develop, the development of the thoracic cage and when pectus excavatum can develop, and how soon in life the mitral valve is capable of being modified to produce regurgitation. I suspect that no one in this room knows the answer to that. I know that I don't, but it is at least conceivable that all three were manifestations of the same underlying process occurring during fetal life.*

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CHRISTOPHER MYERS, MD:† Do you think it is possible that a severe pectus excavatum and scoliosis, and the resulting impingement on the heart, produced a mitral insufficiency murmur?

DR. ROBIN: *Yes. That is not the most common cardiac manifestation of pectus excavatum, but presumably sufficient cardiac distortion can occur to produce mitral insufficiency.*

JAMES THEODORE, MD:‡ What percent of patients who have scoliosis also have mitral regurgitation?

DR. ROBIN: *Well, if you had asked what percentage of patients with scoliosis have murmurs, then I would have said not an insignificant percentage. I would guess at least 20 percent. It is possible for bizarre murmurs to develop, both systolic and diastolic, of loud intensity, which are innocent and merely related to distorted geometry within the thoracic cage. This is well described in the so-called straight back syndrome.[1] Could we go back just a bit? What was felt to be the cause of paroxysmal atrial fibrillation?*

MR. ABUABARA: I do not have any reference to that.

DR. ROBIN: *I see. Suppose you had been her physician then, what would you have thought?*

MR. ABUABARA: Well, after you have pointed out the association with all these other structural deformities, I would have thought of some congenital cause; maybe a second diagnosis would be rheumatic heart disease.

PATRICK HAMMER, MD:§ I think the most logical approach would be to consider rheumatic heart disease; this seemed to be the leading candidate because of the patient's childhood illness; however, it does not rule out other possibilities.

DR. ROBIN: *Yes. In 1967 she was about 51 years old, so it would be a relatively long time between her birth and the development of paroxysmal atrial fibrillation. One would have to ask if this evidence of increasing atrial decompensation was related to mitral insufficiency or whether heart disease is developing independently.*

MR. ABUABARA: She was referred to Stanford University Hospital for a cardiology workup. She had increased shortness of breath and fatigue,

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with many episodes of indigestion. She was treated with digoxin and propranolol. Sector scan at this time showed a percardial effusion and right ventricular enlargement; however, no prolapse of the mitral valve was shown.

DR. ROBIN: *Prolapse was indicated by ultrasound but not by sector scan. What kind of analysis should we use? Either there was prolapse that the sector scan did not pick up; or there was no prolapse which the ultrasound picked up as an artifact; or there was prolapse that had reversed itself and was shown on ultrasound studies but not on sector scan. The decision one has to make, therefore, is which of those possibilities is more likely? That is to say, how often do prolapses reverse themselves, and how accurate is ultrasound versus sector scan in picking up prolapses? You know, if you get conflicting data, you cannot ignore the conflict.*

THOMAS RAFFIN, MD:* By sector scan you mean the new ultrasonic technique which shows a cross sectional image as compared with the old M modes. This new technique produces a much better resolution.

DR. HAMMER: I would guess that the sector scan did not show the prolapse.

DR. ROBIN: *That would be my guess. I do not think that serious prolapse is readily reversed. Early ultrasound techniques are relatively inaccurate; in fact, there are some series that suggest everyone has prolapse of the mitral valve. As you know, there are all kinds of syndromes described as sudden death with prolapse, arrhythmia with prolapse, and the like. Many of these may have been based on cases of patients who really did not have prolapse—the technique used was too sensitive and not accurate.*

ALLAN HANCE, MD:† There is a situation in which one might expect prolapse to be reversed and that is in a person who had 2-mm ST depression, namely papillary muscle dysfunction on an ischemic basis.

DR. RAFFIN: My impression would have to be that the sector scan is more accurate than the M mode echo. Could you tell us why propranolol was being given in the case of the woman we were discussing? Was it for chest pain or for arrhythmia?

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†Fellow in Respiratory Disease.

MR. ABUABARA: The reasons are not clear to us.

DR. ROBIN: *An additional fact, in terms of her cardiac history, is useful. You state that her history indicates the presence of lifelong disease, and she has had one of the best stress tests available for cardiac function—pregnancy. In treating a woman with heart disease, you should obtain, as carefully as you can, a history of occurrences during the patient's pregnancy. Dr. Raffin, what is the natural life history, for example, of valvular heart disease as related to pregnancy?*

DR. RAFFIN: Toward the second and third trimester, especially, women who are pregnant sometimes have problems with decompensation of the valvular heart disease. They need careful follow-up examination in a high-risk clinic because pregnancy may precipitate congestive heart failure.

DR. ROBIN: *Is there a logical explanation for the fact that the most difficulty occurs in about the seventh month?*

DR. RAFFIN: The blood volume goes up significantly during the last trimester.

DR. ROBIN: *It is interesting that if the pregnant patient can be carried past the seventh or eighth month, the actual stress of childbirth can almost always be successfully managed. That is not the time at which the patients have extreme difficulty and die. The process of childbirth, by itself, is much less demanding, and as Dr. Raffin has intimated, difficulty with heart failure correlates well with the curve of plasma volume which rises progressively until the seventh month, and comes down in the last month or two. This is also true of total body water. So, plasma volume, total body water and cardiac symptoms peak in about the seventh month, and then decrease. The old dictum was that if you could carry the patient past the sixth or seventh month, then the patient would do well.*

MR. ABUABARA: The woman had anorexia and a weight change of nine pounds in the last three months. She had no symptoms of heat intolerance, tremors, nervousness, goiter or changes in blood pressure.

DR. HANCE: I am curious about the appearance of the pulmonary artery on the x-ray film of the chest. I realize that there probably is rotation. I would have said that it seems less prominent on the left than on the right and would have inter-

preted that bulge as the left atrium. I think the bulge you see on the left heart border is the left atrial appendage, which does come out relatively high. I just do not see a good pulmonary artery.

DR. RAFFIN: Do you think there is pruning of the pulmonary vasculature?

DR. ROBIN: *Yes.*

DR. RAFFIN: I agree. I think the right side is rather remarkable. You can follow it only about two thirds of the way out.

DR. ROBIN: *Now, there is the other issue as to whether that is atrial appendage or not. It is much too high to be either a pulmonary artery or an atrial appendage. I think all you can say from the x-ray film of the chest is that the right ventricular shadow looks prominent, which is different from saying it is large because the chest is distorted. The left ventricular size appears to be normal and she does not have the aneurysmal dilatation of the left atrium which is associated with far advanced mitral insufficiency. In fact, I think the left atrial shadow is normal, which is almost surprising in view of the gross distortion of the chest. Dr. Newman, would you like to review the catheterization data?*

ANDREW NEWMAN, MD:* The wedge pressure is raised significantly from 10/9/7 (systolic/diastolic/mean) to 19/18/16 torr just on elevating the legs, and the pulmonary artery pressure changed from 25/6/12 to 32/29/26 torr with exercise. On that exercise, which was bicycle exercise on the table, she increased her minute ventilation to only 17 liters per minute.

DR. THEODORE: There has been some increase in the wedge pressure. Do you think that the increase in pulmonary artery pressure is proportionate to the increase in wedge pressure, or do you think that the pulmonary artery pressure goes up higher than can be purely accounted for by the increase in wedge pressure?

DR. NEWMAN: Wedge pressures were measured on leg elevation only. The pulmonary artery pressure is measured on exercise and the wedge pressure is measured just on leg elevation, so we do not have an exercise wedge, which would probably be higher. Anyway, they did selective coronary angiography. The rationale was that the patient had exercise tests with 2 and 3 mm ST segment depression. The coronary arteries were absolutely healthy looking. The left ventricle showed good contraction but early relaxation.

DR. ROBIN: *Were the rest and exercise studies done close to the time that propranolol therapy was stopped? Was it days, weeks or months away?*

DR. NEWMAN: Days.

DR. ROBIN: *Well, there was a substantial increase in wedge pressure. I do not know what to make of it. I could easily visualize that people given propranolol, a myocardial depressant, who have a sudden increase in blood volume, would have a left ventricle that might not respond appropriately and would show an increase in wedge pressure. I think that is an important point. We know that propranolol produces functional impairment of the left ventricle. Once a patient has had propranolol and a change of this kind occurs, I think it is an open issue as to whether the change is due to the drug or due to structural changes in the left ventricle. Can we go back to the catheterization data before we proceed? Another finding in the patient's data which is very peculiar is that the left ventricular end diastolic pressure is zero, and then the pressure rebounds to 28 torr during diastole. I think you can make a pathophysiologic reconstruction of events, especially because the right ventricle tracing shows no end diastolic pressure, with a rebound to only 4 torr.*

DR. RAFFIN: So the patient clearly has left ventricular dysfunction without evidence of right ventricular dysfunction.

DR. ROBIN: *Yes, the tracing is said to show that the left ventricular pressure falls to zero and then rebounds to 28 torr instead of 4 or 5 torr. I think it is also important that this is not happening on the right side. I am going to interpret this as indicating altered compliance of the left ventricle. Similar compliance changes are occasionally seen in cardiac involvement with pectus excavatum or endocardial fibroelastosis, or in diffuse endomyocardial fibrosis or constrictive pericarditis. Generally this is found in both ventricles. My reconstruction is that a major effect of pectus excavatum in this case is to trap the left ventricle and therefore isolated left ventricular disease appears like a restrictive cardiomyopathy or constrictive pericarditis, but is limited to one side (the left). I have never seen that described before in pectus excavatum, so take my analysis with suspicion. Even*

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though the left ventricular end diastolic pressure is zero, a more pertinent finding is that there is a rebound of 28 torr, and if we look at the tracing (if this thesis is correct) then what will be shown is not only a rise to 28 torr, but a series of oscillations as the ventricle first exceeds its elastic limits and then begins to shudder *as the blood fills it. Indeed, if this reconstruction is correct, one might go to the bedside and find a diastolic shudder, a prominent early third sound like a gallop, only much louder. Whether or not that is the mechanism of left ventricular abnormality can be debated. However, the results of catheterization do show one cause of dyspnea: increases in wedge pressure to levels that cause pulmonary edema. Consequently, the patient's dyspnea must stem partly from an abnormal left ventricle.*

DR. NEWMAN: The cardiologists did not make this reconstruction. They were concerned about the patient's extreme dyspnea on exertion and asked us to do pulmonary function studies. Flow rates and helium washout time were normal. We are uncertain whether the volume measurements were accurate.

DR. THEODORE: One thing missing is the diffusion capacity.

DR. HANCE: You said she just could not hold her breath for ten seconds.

DR. THEODORE: Yes.

DR. NEWMAN: At this point, we brought her back for testing at various levels of exercise using the method recommended by the American Heart Association.[2] Basically, exercise is done at four different levels beginning with Bruce 1, 2, 3 and 4. Bruce 0 is 1.2 percent grade at 0 miles per hour; Bruce 0.5 would be 1.7 at 5 miles per hour; Bruce 1 is 1.7 at 10 miles per hour; Bruce 2 is progressing up from that. Most people would reach Bruce 4 with some gasping. Athletes will usually go to Bruce 5. One would expect the patient to go at least to Bruce 1 or Bruce 2. We planned to have her walk or run for seven minutes, but after five minutes she was holding onto the railings with extreme shortness of breath and many complaints. She was unable to continue. At that point, the heart rate was 165 beats per minute and the bicarbonate value dropped to 21 mEq per liter with the pH dropping to 7.38, while Pao_2 remained at 97 torr. At this point you have shown that the patient has been able to maintain oxygenation but circulatory limitation of exercise tolerance is indicated by acidosis. I think this is consistent with what Dr. Robin says about the patient's ventricle; and I think that her problems are, in fact, circulatory and not pulmonary.

DR. RAFFIN: Would you use a pH of 7.38, $Paco_2$ of 35 and a bicarbonate value of 21 mEq per liter as evidence for acidosis?

DR. ROBIN: *Although the change in pH is within measurement error, the change in bicarbonate value is 6 mEq per liter and is significant.*

DR. HANCE: Most people exercised to the point where they must stop because of circulatory limitation would show a greater degree of acidosis than 7.38. This would suggest that in this case there must be other factors stopping the patient, for instance, a rise in wedge pressure and dyspnea on some other basis.

DR. ROBIN: *I do think there is a significant decrease in bicarbonate.*

DR. HANCE: But you and I would not stop exercising at this point. We would be able to go to another level or two.

DR. ROBIN: *Please speak only for yourself.*

DR. RAFFIN: If an increased left ventricular diastolic pressure and pulmonary capillary wedge pressure developed with exercise, it is quite remarkable. The patient's alveolar-arterial oxygen difference increases, but not notably.

DR. ROBIN: *What is more pertinent is that the arteriovenous/oxygen difference increases 5 volumes per dl, a large increase. Moreover hemodynamic measurements show increases in wedge and pulmonary artery diastolic pressure to levels associated with increased lung extravascular water. This implicates pulmonary edema as a factor in the dyspnea and indicates left ventricular disease for which I have supplied a logical (although possibly incorrect) explanation.*

DR. THEODORE: The question you all should ask is, "How do we know she does not have pulmonary limitations rather than circulatory limitations?" I think the point Dr. Newman was making was that although we can argue whether we really pushed her to the limits, there is no one here who would not agree that the drop in bicarbonate is significant and, at least by definition, this would appear to be circulatory limitation. The total

oxygen consumption at that point was significantly less than one would expect for someone her age. Also she never reached two thirds of her maximum voluntary ventilation (MVV). Was she stopped because of some kind of intrinsic lung disease? Is this why she could not reach her MVV? When you look at this case, you see that the blood gas values certainly do not bear that out. If anything, the $Paco_2$ dropped as the Pao_2 increased. All we have is an increase in physiologic dead space, and that could certainly be consistent with some kind of abnormality within the pulmonary circulation.

DR. ROBIN: *People stop exercising for many different reasons. Patients with mild degrees of lactic acidosis, for example, may stop exercising because they are neurotic, as well as having pulmonary edema develop. Poorly conditioned patients may show an early pulse from lactic acidosis. I suspect that patients treated with propranolol may show premature lactic acidosis. The latter possibility is important in this patient: biochemical evidence of circulatory impairment develops as a relatively early degree of increased oxygen consumption, and with our knowledge that should be interpreted as circulatory limitation.*

DR. RAFFIN: When the patient's ventilatory response to exercise changes from 3.14 to 33.5 liters per minute, about 25 percent to 30 percent of the MVV, do you think the response is inappropriate for that amount of exercise? Gradually some lactate acidosis was shown.

DR. ROBIN: *Dr. Lynne-Davies should comment and then I will give you my opinion. What percentage of the MVV does one usually mobilize during peak exercise?*

PATRICIA LYNNE-DAVIES, MD:* Well, allegedly 65 percent, something in that order, but there are one or two peculiarities in this case. First, the tidal volume at rest is extraordinarily low even for someone who is fairly small. Consequently, she has a spectacular increase in tidal volume with exercise. Second, although it may well be true that her lung volumes are normal, it is interesting that the ratio of residual volume to total lung capacity is elevated, and the functional residual capacity is mildly elevated. I think you also found a functional residual capacity that was high. So I think that there may well be some limitation. There is no question that one does not function as well at 60 percent or 70 percent total lung capacity as you do at 50 percent, just in terms of mechanical ability to shift ventilation around. Having said all of that, I still do not think these are in any sense limiting factors. I am impressed, just as Dr. Robin has been, by factors like the increase in her arteriovenous oxygen pressure difference with exercise. These seem much more dramatic to me.

DR. ROBIN: *Given the general issue of lungs versus circulation, I do not think it is possible to say that the patient has perfectly normal lungs. Indeed, given mitral stenosis or coronary artery disease, which is hemodynamically significant, you will almost never find normal lungs. At times you will find problems we generally consider representative of obstructive lung disease. After all, the mucosae of the bronchi become edematous and bronchiolar changes occur with pulmonary edema.*

I believe the main focus of this patient's disorder is circulatory for two reasons; objective measurements show that the circulation is primarily impaired, and we can come up with a logical explanation for the impairment. A handle for discussing this case is to ask, "What happens in patients who have severe pectus excavatum, even without scoliosis?" In most patients, nothing happens. If you measure lung function and cardiac function not only when, for instance, the patient is young, but continue to make measurements, the interference of the pectus excavatum with the function of either the heart or the lungs is minimal or nonexistent.

That brings up another point. If you look at 100 patients who have had a surgical operation for pectus excavatum the overwhelming indication is cosmetic. It is interesting that the surgical procedure for the disorder is bloody and complicated. In one way, pectus excavatum in most patients represents an imbalance between a surgical procedure for something cosmetically wrong with the patient and a surgical procedure for physiologic indications. In a small number of patients with the disorder restrictive lung disease develops, and the restriction is pretty clearcut; it is not as tenuous as in this patient. The pectus excavatum is usually severe and notable reductions are seen in all lung volumes. Such patients have rapid, shallow breathing and the natural life history, as far as I know, is not progressive. Patients first present with com-

*Associate Professor of Medicine.

plaints of dyspnea, and there are examples in which surgical treatment relieves restrictive lung disease.

Another complication more or less well documented in the literature is restrictive heart disease, and up until now my view is that it appears like chronic restrictive pericarditis, endomyocardial fibrosis or endocardial fibroelastosis. Both sides of the circulation are involved, with generally an equalization of pressure across both. When right ventricular catheterization is carried out in the patient there is a right ventricular diastolic dip (square root sign). Not uncommonly you hear the so-called pericardial knock, which is not necessarily pericardial in origin. These patients may have severe congestive heart failure. The biventricular heart disease can be treated by surgical operation, which corrects the pectus excavatum.[3]

Pulmonary hypertension may represent another complication. One patient with severe pulmonary hypertension and pectus excavatum made a profound impression on me. This was a woman in her late 20's who was married to an Army officer in Hawaii. Her husband went to see his physician each year for an examination that included an exercise test. She accompanied her husband to the physician's office and when the husband finished the exercise test she asked if she could try it. She mounted the treadmill, took about four steps and fainted. It was clear that she had severe heart disease. An x-ray film of the chest showed a pronounced pectus excavatum, and cardiac catheterization showed severe pulmonary hypertension with pulmonary artery pressures equal to systemic pressures. Findings on pulmonary angiograms were normal and the patient had the usual kind of workup for pulmonary hypertension, which showed nothing. Primary pulmonary hypertension was diagnosed.

It occurred to me that there could well be a pathogenetic link between the pectus excavatum and the development of severe pulmonary hypertension. The pathogenetic link could be explained by what we have called the Goldblatt lung.[4] *Under several clinical circumstances, there is the development of pulmonary hypertension in patients who have reductions, without cessation, of regional pulmonary blood flow over a long period. In going back to the concept of primary pulmonary hypertension, there are two important features, one of which is not usually considered: increases in pulmonary artery pressure that occur without a known cause and the development of a disproportionate degree of pulmonary hypertension for any given degree of heart or lung disease.*

If you go back to the basic relation between mean pulmonary artery pressure and flow in a normal lung, the flow must double to produce an increase in pressure. There are three or four conditions in which there is less than 50 percent of the pulmonary vasculature involved in disease of the lung or the pulmonary apparatus, but in which the patient has severe pulmonary hypertension that is disproportionate. This may occur in unilateral pleural fibrosis. We collected a series of four cases, and there now have been about three or four more reported in the literature—cases of unilateral pleural restriction with severe pulmonary hypertension.[4] *The question is, if the disease involves only one lung, why is the pulmonary artery pressure elevated? The second condition that fits this classification is multiple regional pulmonary coarctations. There are well described cases in which there are multiple small pulmonary artery coarcts as a congenital defect.*[5] *The degree —that is, the number of vessels involved—is not of the magnitude which would generally occlude greater than 50 percent of the pulmonary vasculature. These patients may have striking pulmonary hypertension, in fact, that is one of the clinical features. The third condition is kyphoscoliosis; progressive pulmonary hypertension may develop in patients with this condition even if there are no overt difficulties with breathing.*[6]

Dr. Liebow, impressed by this phenomenon, reported neural elements which he described as neuroepitheliomas in the lungs of these patients. He hypothesized that the neuropithelioma might be the site of the release of a humor that produced generalized pulmonary hypertension. Therefore, when I saw the patient with pectus excavatum and pulmonary hypertension, I wondered whether the disorders could possibly be related. On an intuitive level, it was convincing enough to suggest that the patient, at age 27, has pulmonary artery pressures equal to systemic pressures. The length of life she had left, at least statistically, was short and there was already, when I saw her, right ventricular failure and functional tricuspid insufficiency. One possible therapeutic approach was to correct the pectus excavatum. Two other experts (if I qualify as an expert) were consulted and they felt that my suggestion was outlandish. Nothing was done.

If my reconstruction is correct, pectus excava-

tum in this case represents a form of cardiac restrictive disease in which the anatomical restriction is largely localized to the left ventricle; therefore, the usual bilateral signs of restrictive cardiac disease related to the disorder are not shown. However, pectus excavatum does restrict her cardiac output during exercise, and gives her periods of pulmonary edema when she is exercising or has increases in blood volume. Her case, therefore, represents isolated left ventricular disease in which, conceivably, the prolapsed mitral valve might have an additional role.

However, the major problem is related to mechanical restriction of the left ventricle. In addition, the patient is being treated with propranolol, which depresses myocardial contractility. If it is true that the problem is related to mechanical restriction (and it is easy to persuade yourself that a logical explanation is true) then this case represents another unusual complication of pectus excavatum. Then the question is what should be done? Clearly, therapy with propranolol should be stopped because it would render a noncompliant left ventricle even less compliant. If that failed, one might consider relieving the disorder surgically and freeing the left ventricle. I would argue against this for two reasons: The first is that the surgical operation is difficult and is usually a four- to five-hour procedure with major blood loss in which the sternal plate is unroofed by cutting the ribs and lifting the sternum. A prosthetic device is inserted and the sternal plate is sewed in place. The second reason is that the case makes clear physiological sense to me. This is dangerous; when a case fits into a neat package you should suspect the analysis.

DR. HANCE: Another possible diagnosis is restrictive heart disease, also associated with unilateral signs that are left sided only. This is now referred to at the National Institutes of Health as asymmetrical septal hypertrophy, and I think it fits this case fairly well. The onset occurs when patients are in their 50's. In some cases, tachyrhythmia may be a problem and the kind of limitation would be highly suspicious of that. Prolapse of the valve may frequently be associated with it. This narrowing of the ventricular neck is highly suggestive. So, I would do a regular echo scan rather than a sector scan, and would look closely for that abnormality.

DR. ROBIN: *I do not object to that diagnosis, but I really think the problem is that the referring physicians have used all their techniques, and cannot explain left ventricular disease on the basis of their data. Maybe the reason is that they (like we) are dealing with something that has not been described previously.*

DR. HANCE: Is asymmetrical septal hypertrophy a common diagnosis in the cardiology clinic here? That has not been my impression. This is a case in which you might have a pathologic abnormality without obstruction.

DR. RAFFIN: Just as in most of Epstein's recent work in trying to study the epidemiology of prolapse, asymmetrical septal hypertrophy is a diagnosis made easily on just the A mode ultrasound.

DR. ROBIN: *My guess would be that septal hypertrophy or idiopathic hypertrophic subaortic stenosis could have been pulled out of the data had the data been suggestive; that does not necessarily mean that people have looked for it specifically.*

DR. RAFFIN: I would like Dr. Newman to get the pressure tracings. This case is fascinating if you really do have the classical square root sign of some types of restrictive cardiac abnormalities; if you do not, then the case is still interesting, but less elegant, I think.

In the August 5, 1972, issue of the *New England Journal of Medicine* there is a report of a series of patients with pectus excavatum who were operated on for significant restrictive heart disease or symptoms due to the disorder. It is interesting that patients were more symptomatic when sitting than when supine, and this was thought to be the result of the heart dropping down further into the pectus.[7]

DR. ROBIN: *That form of dyspnea is called platypnea.*[8]

DR. RAFFIN: It is not completely clear to me that surgical operation is inappropriate for this woman if her quality of life is zero.

DR. ROBIN: *The decision should not only be based on the quality of life. It should also be based on the security of feeling that your analysis is accurate. This is an important point because we are increasingly carrying out tests in patients because of insecure feelings that stem from inadequate knowledge. If I were certain that my analysis was correct, or that it had eight chances out of ten of being correct, then I might be enthusiastic*

about using a surgical procedure. Confronted by a patient who is one in the world, and to come up then with an unprecedented indication for surgical operation would be arrogant. A bad guess might cost the patient some years of relatively happy life. I am certain I would begin by stopping the propranolol therapy.

In summary, we have seen a patient with severe pectus excavatum and dyspnea. It seems unlikely that the manifestations are related to abnormal pulmonary mechanics, but rather to abnormal cardiac function. Pectus excavatum can produce restrictive lung disease, restrictive heart disease and possibly pulmonary hypertension (by a Goldblatt mechanism). The hemodynamics suggest restrictive left ventricular disease that may have been intensified by the use of propranolol. After much soul-searching, the consensus would be to stop propranolol therapy and see what happens.

FOLLOW UP: Review of the patient's cardiac tracings showed what seemed to be a *square root* sign with oscillations following the diastolic dip in the left ventricular tracing. This was considered by most (but not all) to indicate restrictive left ventricular disease. Propanolol therapy was stopped and the patient's condition has improved, but not to the point where she can tolerate normal exercise. However, she is considerably more comfortable.

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Refer to: Cello JP: Gastroesophageal variceal hemorrhage—Pathogenesis and management—Medical Staff Conference, University of California, San Francisco. West J Med 130:531-539, Jun 1979

Gastroesophageal Variceal Hemorrhage

Pathogenesis and Management

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Associate Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, CA 94143.

DR. NAUGHTON:* *The topic for consideration today is variceal hemorrhage. We have asked Dr. John P. Cello, Chief of Clinical Gastroenterology of San Francisco General Hospital, to discuss the topic, with Dr. Robert Byers first presenting a case recently seen on the medical service.*

DR. BYERS:† The patient is a 62-year-old white woman with an approximately two-year history of hyperthyroidism. She was seen by her physician one year before admission here for epistaxis and palmar erythema. Hepatomegaly was noted together with abnormal findings on liver function tests. Results of a biopsy of the liver done at that time were interpreted as mild persistent hepatitis. The patient was treated with prednisone in a tapering dosage to 10 mg a day for the last four months. She was admitted to a local hospital for hematemesis and melena 1½ weeks before admission here; endoscopy at that time showed blood loss from varices. She was given a transfusion of 6 units of blood and sent home, but two days following discharge she returned to the local hospital with orthostatic hypotension and black stools. She was given another transfusion of 6 units of blood and was transferred to the University of California Medical Center. She had no history of alcohol abuse. She was well developed, well nourished and in no acute distress; she was alert and cooperative. Vital signs were normal and without orthostatic changes. Spider telangiectasias on the trunk and upper arms were noted, bibasilar rales were present on examination of the chest, and examination of the abdomen showed the liver to have a 12-cm span in the midclavicular line extending 2 cm below the right costal margin. A firm, tender hepatic edge was palpated. The spleen tip was felt. Ascites was not noted, but palmar erythema was obvious. All stool specimens were melenic.

Laboratory studies on admission disclosed the following values: leukocytes, 11,000 per cu mm; hematocrit, 29.2 percent; total bilirubin, 1.3 mg per dl; serum alkaline phosphatase, 38 units per dl; lactic dehydrogenase, 173 units per ml; serum glutamic oxaloacetic transaminase, 50 units per ml. Other laboratory values were normal and a study was negative for hepatitis B surface antigen. A radiograph of the chest showed an elevated right hemidiaphragm and small right pleural effusion.

The hospital course was marked by a drop in hematocrit to 25.7 percent and a transfusion of 1,000 ml was required. Endoscopy showed large esophageal varices without fresh blood loss. Some ascites was found on abdominal sonography. Examination of a biopsy specimen of the liver

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†Robert Byers, MD, Medical Resident, University of California, San Francisco.

showed cirrhosis without hepatitis. The patient was transferred at that time to the surgical service, where a splenorenal shunt operation was carried out without complications. She was discharged and she returned home to the care of her private physician.

Dr. Cello:* A slightly more prosaic clinical description of a patient with portal hypertension was recorded in the 17th century. John Brown, Royal Physician at St. Thomas Hospital in London, was the first clinician to describe the appearance of the liver in a patient with portal hypertension and gross ascites.[1] In 1685 Brown wrote "I send you here the figure of a hydropical (that is, an ascitic) person. He was about 25 years of age, a soldier in one of His Majesty's regiments here in town who contracted his distemper by drinking much water, when he could not stir from his duties and catching cold at night in being upon the guard. His swellings resumed so there was nothing more now to be thought of but a paracentesis, whereby we drew from the patient three pints of brinish liquor and within three days as much more; the next day he died." Brown describes the appearance of the liver as follows: "The liver consisted in its concave, convex and inward parts of glands which made up the whole substance." However, it was René Laennec who first used the term "cirrhosis" in 1826 to describe the gross appearance of the liver in a patient with portal hypertension and ascites. He coined the word *cirrhosis,* from the Greek *scirrhus,* meaning of yellow or tawny color.[2]

There are several aspects of portal hypertension and variceal hemorrhage that should be considered. First, I shall review our understanding of the pathophysiology of portal hypertension and the development of gastroesophageal varices. Second, and quite distinct from the first (because we know that there can be varices in patients for years without blood loss), I shall consider the pathogenesis of the actual torrential hemorrhagic episode as a complication of varices. Third, some aspects of the medical and surgical management of esophageal varices will be reviewed.

Pathophysiology of Portal Hypertension

The liver begins an intimate relationship with portal venous blood (blood returning from the bowel) early in embryonic life when the ventral hepatic diverticulum develops from the foregut invading the omphalomesenteric vein. This embryonic vein receives blood from the yolk sac, a structure continuous with the primitive gut. The omphalomesenteric vein of the embryo eventually becomes the portal vein in adults.

With the body at rest, between digestive periods, total hepatic blood flow in an adult is 1,500 ml per minute, or roughly 58 ml per 100 grams of liver per minute. This represents 28 percent of the cardiac output and 20 percent of the total oxygen utilization of the body at rest. During digestion, arterial-portal venous oxygen differences are notably increased due to increasing utilization of oxygen in the intestine, and the increased oxygen demand by the liver during digestion is supplied by increasing hepatic arterial blood supply. Of the 1,500 ml per minute of total hepatic blood flow, 1,000 ml, or two thirds, is portal venous flow. In addition, portal venous blood supplies 50 percent to 60 percent of the total oxygen utilization of the liver at rest. This important portal flow is perfused at a central portal venous pressure of 10 to 15 cm of water. The portal venous blood delivery system, therefore, is a high volume, low resistance system.

In this high flow, low pressure system, any lesion in the portal venous delivery system may increase portal venous resistance and lead to portal hypertension. According to Dame Sherlock and many other investigators, one can conveniently classify portal hypertension on the basis of the site of increased portal venous resistance.[3] In extrahepatic portal hypertension, classically one is dealing with either portal venous occlusion in which splenic or main portal veins are thrombosed or increased splenic blood flow due to an arteriovenous malformation or even to massive splenomegaly. Intrahepatic presinusoidal portal hypertension will occur in cases of schistosomiasis, in congenital hepatic fibrosis or with a variety of portal zone-infiltrative processes that can notably increase portal venous resistance. Sinusoidal portal hypertension and postsinusoidal portal hypertension are seen in a variety of processes such as cirrhosis and veno-occlusive disease of the liver.

Ordinarily the most common cause in the development of hypertension in our society is alcoholic liver disease (Table 1). Actually at a variety of stages in the development of alcoholic liver disease, one can find increasing portal venous resistance. Cirrhosis, however, is the stage

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TABLE 1.—*Causes of Portal Hypertension in 100 Consecutive Patients Admitted to the University of California Medical Center, San Francisco, and Affiliated Hospitals, for Portal-Systemic Shunts, 1974-1978*

Alcoholic Liver Disease	
Active alcoholic	75
Past alcoholic	10
HB_sAg^- macronodular cirrhosis	7
HB_sAg^+ macronodular cirrhosis	2
Hemochromatosis	2
Schistosomiasis	2
Wilson disease	1
Portal vein thrombosis	1
TOTAL	100

HB_sAg = hepatitis B surface antigen

in which there is a substantial irreversible component of portal hypertenson. The most important component of portal hypertension in the cirrhotic liver is the regenerative nodule.[4] Several factors are responsible for this.[5] The nodule is supplied almost exclusively by the hepatic arterial system. New portal venous tributaries are not grown in the hepatic tissue in the nodule. As the nodule grows and enlarges, it will first compress hepatic venous structures. Therefore, the nodule tends to produce a postsinusoidal portal hypertension. In addition, the nodule by its growth and enlargement will compress and distort the remaining normal parenchyma perfused by the portal vein. Consequently, increased sinusoidal resistance to portal flow occurs. A third factor in the development of portal hypertension in nodular regeneration is the formation of small hepatic arterial-to-portal-venous shunts in the broad bands of scar tissue between nodules.

Varices—One of Several Shunts

Whatever factors are responsible in portal hypertension—be they presinusoidal, sinusoidal or postsinusoidal, alcoholic liver disease, or postnecrotic cirrhosis—the most clinically notable sequela of cirrhosis, other than hepatic failure, is the development of a large number of portal-venous to systemic-venous shunts. The most clinically significant shunts are those that occur at the gastroesophageal junction (producing varices), the umbilicus (producing the caput medusae) and the rectum (as large internal hemorrhoids). Other clinically insignificant but occasionally prominent shunts occur around the diaphragm and around the spleen.

The most important of these shunts are those

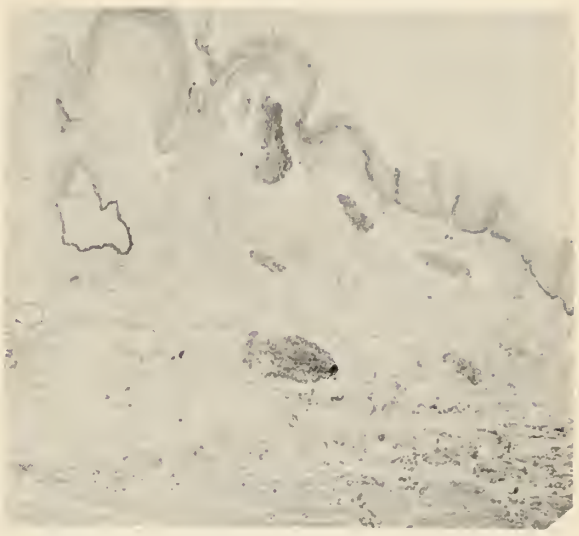

Figure 1.—Esophageal varices. Thin-walled venous channels are noted in the submucosal loose connective tissue. Only the stratified squamous epithelium of the esophagus separates the portal blood from the lumen.

that develop at the gastroesophageal junction, where, through increased resistance to portal flow, a large number of potential venous channels open. These channels, in fact, are simply the submucosal venous channels (the venous plexus) that are ordinarily found in the submucosa of the tubular gastrointestinal tract. Under the influence of portal hypertension, portal venous flow is channelled from a relatively high resistance region in the liver to the relatively low resistance system that is adjacent to the esophagus; namely, the azygous and hemiazygous systemic-venous systems. These variceal venous channels, therefore, are not newly formed, but rather massively dilated, submucosal venous channels made up of extremely thin-walled vessels that are precariously approximated to the lumen of the esophagus (Figure 1). Endoscopically, varices appear as large, soft, fleshy and tubular nodular masses that run longitudinally down the esophagus. In some patients the varices are so prominent that they touch each other across the lumen and may almost completely occlude the lumen.

Varices, therefore, commonly develop in patients with portal hypertension. However, we know that there can be portal hypertension and varices in patients for years without blood loss. Moreover, there can be hemorrhage from varices that is followed by a relatively quiescent period of many months. Because variceal hemorrhage is the most life-threatening consequence of cirrhosis,

TABLE 2.—*Pathogenesis of Variceal Hemorrhage in Cases of Portal Hypertension*

Site—esophagus (from 20 to 40 cm from incisors); stomach: gastric varices high in cardia or fundus
Pathologic condition—small punctum or erosion; no esophagitis, ulcer or laceration
Factors responsible—unknown/undocumented • hypotension of lower esophageal sphincter and reflux esophagitis • Mallory-Weiss tears over a varix • esophageal/gastric peptic ulceration • surging increases in portal-pressure Valsalva maneuvers, straining, coughing, increasing ascites

what can be understood about the factors responsible for hemorrhagic episodes?

We know from studies of patients and epidemiology that the site of blood loss is invariably in the distal esophagus or proximal stomach (see Table 2); consequently, the proper term to describe this blood loss would be gastroesophageal variceal hemorrhage. The pathologic condition at the time of endoscopy or postmortem examination is a punctum or small isolated erosion. It is uncommon to see esophagitis, an ulcer or a laceration. What factor is responsible? There are a variety of theories that have been proposed to explain the development of the actual bleeding episodes. Is there hypotension of the lower esophageal sphincter that allows reflux of gastric acid and reflux of esophagitis overlying the varix? Is there a Mallory-Weiss tear, a longitudinal linear tear in the mucosa overlying the varix? Is it peptic ulcer? The factors responsible are not defined but some of these questions can be answered. In spite of the massive ascites possible, there is no demonstrable hypotension of the lower esophageal sphincter in those patients in whom studies have been done shortly after an exsanguinating variceal blood loss. Before and after diuresis, the mean pressure of the lower esophageal sphincter in these patients is normal.[6] This is further supported by our endoscopic and pathologic correlations. Esophagitis is not commonly found on endoscopy in the region of a varix from which there is blood loss. Moreover, rarely do we encounter Mallory-Weiss lacerations in the region of variceal hemorrhage. Peptic ulceration is also not commonly found. However, we know that there is no blood loss from varices unless intravenous pressures rise to dramatic levels, possibly associated with straining, coughing or Valsalva maneuvers. In addition it appears that exsanguinations requiring control through surgical therapy are unlikely to occur unless the portal venous pressures surge above 45 to 50 cm of water.

Diagnosis

Given our understanding of the pathogenesis of portal hypertension and variceal hemorrhage, how should these conditions be diagnosed? Is there any way one can suspect, from a patient's presentation, that an episode of blood loss is variceal in nature? Usually variceal hemorrhage is sudden and voluminous with hematemetic episodes unassociated with epigastric pain. On occasion, hemorrhage is less dramatic, such as was seen in the case under discussion, in which several days of painless melena were noted. The latter aspect of variceal hemorrhage was generally not appreciated until endoscopy was carried out routinely and we noted large eroded varices in patients presenting with several days of melena. On physical examination, as exemplified in this case, portal hypertension may or may not be suggested. Patients with variceal hemorrhage may have *no* clinically detectable ascites, or other signs of cirrhosis or portal hypertension. In addition, on physical examination the finding of features suggestive of chronic liver disease and portal hypertension *does not* substantiate varices as the cause of hemorrhage. No laboratory test is specific for cirrhosis and portal hypertension, and even standard single-contrast upper gastrointestinal series may fail to detect varices radiographically in 60 percent of the cases. Moreover, detection of gastroesophageal varices on barium studies does not confirm them as the site of hemorrhage.

Endoscopy is the only practical method for confirming varices as the site of upper gastrointestinal hemorrhage. The ideal time for carrying out this examination is shortly after a patient has arrived at the hospital and his condition has been stabilized. Large blood clots that will obscure vision must be evacuated from the stomach. When the stomach is clean, fresh blood loss from a punctate area overlying a varix, or an adherent fresh clot on a varix, confirms the site of hemorrhage.

Initial Medical Therapy

Variceal hemorrhage is not a minor problem in San Francisco. Every year 30 to 50 patients with variceal blood loss are admitted to San Francisco General Hospital (Table 3) and 14

TABLE 3.—*Causes of Significant Upper Gastrointestinal Hemorrhage, San Francisco General Hospital (100 consecutive cases)*

Lesion	*Documented by Endoscopy*
Esophagitis	4
Esophageal cancer	1
Esophageal varices	14
Mallory-Weiss tear	13
Total esophagus	32
Gastric ulcer	20
Gastritis	14
Gastric cancer	3
Pyloric channel ulcer	6
Total stomach	43
Duodenal ulcer	22
Duodenitis	3
Total duodenum	25
TOTAL	100

percent of the episodes of significant upper gastrointestinal hemorrhage occur in varices. The latter figure is verified in other series in urban populatons.

What should be the approach in cases in which blood loss is thought to be from varices, particularly in patients with florid stigmata of chronic liver disease? Obviously resuscitation is the first step; little can be done or should be done diagnostically unless the patient's condition is first hemodynamically stabilized. Certainly in many cases in which there is blood loss from varices, several units of blood are lost and prompt fluid replacement is required. However, with the attempt to restore intravascular volume, many patients who have had blood loss from varices are overhydrated or hypertransfused. In principle this would not appear to be hazardous in these patients. However, some experimental data suggest that there is a unique intravascular volume-portal pressure relationship in patients with cirrhosis, particularly in those with ascites in whom the ability to accommodate excess amounts of fluids is limited; this is manifested by surging increases in portal pressure in patients with volume overload.[7,8] Because a patient with ascites and cirrhosis is unable to accommodate extraordinary amounts of volume replacement, it is generally recommended that the central venous pressure be kept below 5 cm of water. In elderly patients or patients with cardiopulmonary disease, the central venous pressure may not accurately monitor left-heart filling pressures and may incorrectly estimate intravascular volumes. In these circumstances thought should be given to placing a Swan-Ganz pulmonary artery catheter.

TABLE 4.—*Proper Usage of Vasopressin (Pitressin) for Variceal Hemorrhage*

Preparation: use only aqueous vasopressin, not oil.
Route: intravenous continuous infusion
no need for intraarterial dose
Dosage: range for 70-kg man—
0.1 to 0.4 units per minute.
no loading dose
no tapering needed
Patient location: intensive care environment
Major side effects: depressed cardiac output,
hypertension,
coronary ischemia

In many cases in which hemorrhage is great, vomiting and water lavage may contribute to pulmonary aspiration. It may be necessary to place an endotracheal airway to preclude aspiration. Elective intubation of a patient may be of additional benefit. Because many of these patients are agitated, uncooperative and alcoholic, diagnostic endoscopy and even placement of a balloon tamponade will be facilitated by airway intubation and muscular paralysis induced by pancuronium bromide or succinylcholine chloride.

Vasopressin Therapy

Vasopressin therapy is effective in moderating severe hemorrhage from the gut. The site of action of vasopressin infusion in patients with variceal blood loss is the splanchnic arteriolar bed, and not the varix. There is no vasopressin-responsive vascular smooth muscle in the portal venous system. At the level of the splanchnic arteriole, a relatively nonspecific vasoconstriction occurs with vasopressin therapy. This splanchnic oligemia induced by vasopressin causes a notable decrease in portal venous flow and pressure. There is no effect of vasopressin infusion on the hepatic artery. In fact, in some recent studies it is documented that with the decrease in portal venous flow, the hepatic artery alone in the splanchnic bed actually vasodilates, maintaining near normal total hepatic blood flow.

How should one administer vasopressin (Table 4) to a patient with variceal hemorrhage? Results of studies using rhesus monkeys, show that there is a stepwise decrease in superior mesenteric arterial blood flow, and a concomitant decrease in portal venous pressure as one increases vasopressin infusion logarithmically.[9] Earlier clinical experience

suggested that selective arterial infusion of vasopressin into the left gastric artery was necessary. The efficacy of selective intraarterial vasopressin infusions has been shown in recently published primate studies employing electromagnetic flow meters and manometers in the superior mesenteric artery and portal veins. The intraarterial infusion of 5 mU of vasopressin per kg of body weight per minute results in a prompt decrease of the arterial blood flow and portal venous flow, and a profound drop in portal venous pressure. At this low dose—equivalent to 0.35 units per minute infusion of vasopressin in a man weighing 70 kg (154.3 pounds)—systemic side effects could be shown with an elevation of central aortic blood pressure and a decrease in cardiac output.[9] Thus, continuous intraarterial vasopressin therapy, while effective in decreasing portal flow and pressure, does have undesirable systemic side effects (Figure 2A).

With continuous systemic intravenous vasopressin infusion at the same dose in primates (5 mU per kg of body weight per minute), comparable effects on splanchnic arterial flow and portal pressures are shown. A prompt decrease in superior mesenteric arterial blood flow, an increase in peripheral vascular resistance, and a prompt decrease in portal venous flow and pressure occur with intravenous infusions (Figure 2B). Systemic side effects are comparable whether the dose of vasopressin is administered intraarterially or intravenously.[10,11]

Our recommendation, based on these and other studies and on clinical experience, is that the vasopressin be administered by continuous intravenous infusion at a dosage of approximately 5 mU per kg of body weight per minute. Thus, we would recommend administering between 0.1 and 0.4 units per minute in an adult, as a continuous intravenous infusion. The onset of action is so prompt that no loading dose is necessary, and no tapering is needed when administration of the drug is discontinued. Another important clinical point is that toxicity of vasopressin is definitely related to systemic blood levels. The drug has extraordinary toxicity in some patients with hypertension, low cardiac output and coronary ischemia shown by ischemic changes on an electrocardiogram. Therefore a patient's condition should be closely monitored while vasopressin is being administered. The toxicity is relatively unpredictable. In some elderly patients a full effective dose of vasopressin infusion may be administered without any problems, while in some younger patients significant coronary ischemia occurs.

Balloon Tamponade

Sengstaken-Blakemore and Linton tubes have been used for years in patients with massive blood loss from varices. So much morbidity and mortality has been associated with the use of balloon tamponade therapy in cases of hemorrhage from esophageal varices that, in some centers, the use of balloon tamponade has been abandoned in favor of vasopressin infusion or emergency surgical operation. Our experience at hospitals affiliated with the University of California, San

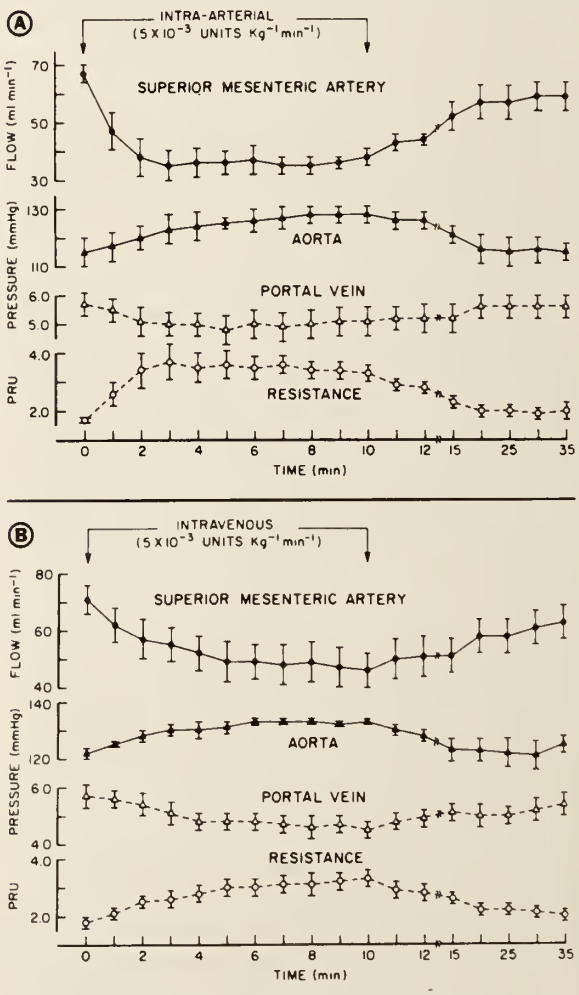

Figure 2.—Vasopressin administered to five monkeys intraarterially **(A)** or to six monkeys intravenously **(B)**. The infusions begin at minute 0 and continue for ten minutes. Superior mesenteric artery blood flow fall in both situations within a few minutes of infusion. (Reproduced with permission from Freedman AR, and *Gastroenterology.*[9])

TABLE 5.—*Suggested Physician Orders for Maintenance of Minnesota Balloon Tamponade*

1. Chest radiograph, portable, to document subdiaphragmatic location of gastric balloon.
2. Keep gastric balloon inflated with 400 ml air; double-clamp inflation port; *do not deflate.*
3. Apply tension to balloon by taping insertion tube to corner of mouth, using crossed wooden tongue blades, cushioning mouth with gauze.
4. Change tube position from one corner of the mouth to the other every four hours.
5. Esophageal suction port—intermittent suction; *never lavage via this port.*
6. Gastric suction port—maintain on low intermittent suction; may lavage and administer antacids/lactulose via this port.
7. Esophageal balloon (if necessary)—inflate with air monitoring pressure using aneroid manometer. Never inflate above 40 mm of mercury. Deflate esophageal balloon for 30 minutes every six hours.
8. Keep patient without oral intake.
9. Elevate head of bed 15 degrees.
10. Encourage good mouth care and frequent deep breathing.
11. Tape scissors near bedside. If respiratory distress caused by tube, cut entire tube assembly and remove immediately.

Francisco, Medical Center has been positive. The tamponade is effective in arresting torrential hemorrhage from varices and allows hemodynamic stabilization in almost all cases, even in those ultimately requiring emergency surgical therapy . These favorable results are explained by our restricting the insertion and maintenance of tamponade to patients who have endoscopically proven blood loss from varices, and by requiring that the procedure be done by a senior gastroenterology or surgical resident. The most common cause of morbidity associated with the use of balloon tamponade in other series is aspiration pneumonia. Several advances in the design and construction of newer balloons have helped make this complication less likely. The Minnesota tube, the balloon tube now in use at the three hospitals affiliated with the University of California, San Francisco, has incorporated into the insertion tube, a separate lumen for aspirating esophageal secretions. With Linton or Sengstaken-Blakemore balloons inflated, occluding the gastroesophageal junction, pharyngoesophageal secretions and blood could pool in the esophagus and spill over into the trachea. The esophageal suction ports in the Minnesota tube, however, can prevent this and, therefore, we believe that it is the instrument of choice for maintaining balloon tamponade. To maintain effective airway cleansing in patients with vigorous hemorrhage from esophageal varices, intubation is carried out before the insertion of tamponade balloons. Strict orders should be written and carried out for care of patients receiving balloon tamponade therapy (see Table 5). Another interesting aspect of the new Minnesota balloon has been successful tamponade of esophageal varices through the use of gastric balloons alone. By inflating a gastric balloon with 400 ml of air and applying gentle traction to the mouth, the gastric fundic varices supplying blood to the esophageal varices are compressed and esophageal balloons almost never have to be used. The latter aspect of the balloon tamponade, esophageal balloon inflation, is the most difficult to maintain and has been associated with esophageal ulceration and perforation. In our experience, the large gastric balloon of the Minnesota tube has been highly effective alone in arresting variceal hemorrhage.

Balloon tamponade is a temporizing procedure, but one that allows for more careful preparation of patients for surgical operation. In 85 percent of patients in whom balloon tamponade is used, hemorrhage will be controlled. However, in a small percentage of patients, balloon tamponade is ineffective. Following deflation of the balloon, blood loss will occur again in a high percentage of patients, necessitating reinsertion of the tube. Tamponade with esophagogastric balloons is an effective hemostatic maneuver, and not the primary therapy for hemorrhaging from varices. However, in our experience it is unusual for varices to continue bleeding in spite of the use of vasopressin alone, or in combination with balloon tamponade.

Surgical Therapy for Variceal Hemorrhage

Variceal hemorrhage is often severe, occurs and recurs unpredictably, and is difficult to treat quickly. Because of these factors, surgical decompressive procedures have been devised to reduce portal hypertension. Originally called Esk fistula, portal-systemic shunts have been developed over the years and include a variety of innovative decompressive procedures. The most commonly used are end-to-side and side-to-side portacaval shunts, and splenorenal shunts. In patients with large cirrhotic livers, a variation of the side-to-side portacaval shunt can be constructed by using a graft of Dacron or autogenous jugular vein. This "H-graft" or Drapanas mesocaval shunt is often used at San Francisco General Hospital

TABLE 6.—*A Partial Listing of Factors Showing Association With Favorable Outcome Following Portal-Systemic Shunts*

Favorable Survival Factors*
Younger patients
Good nutritional status
Good muscle mass
Nonencephalopathic before shunt
No notable ascites
Nonalcoholic liver disease
Abstaining from alcohol
No chronic active hepatitis or alcoholic hyaline on biopsy
Albumin >3.0 grams per dl
Bilirubin <2.0 mg per dl
Prothrombin < two seconds prolonged
Serum glutamic oxaloacetic transaminase <100

*Composite series from multiple sources—not universally agreed upon by all investigators.

TABLE 7.—*The Child's Classification, Widely Used by Clinicians in Assessing Heptatic Functional Reserve in Patients With Cirrhosis*

	Status		
Test	*A*	*B*	*C*
Bilirubin (mg per dl)	<2	2-3	>3.0
Albumin(grams per dl)	>3.5	3.0-3.5	<3.0
Ascites	None	Easily controlled	Pronounced
Neurologic status	Alert	Early encephalopathic state	Coma

in patients in unstable condition.[12] Clotting in the prosthetic Dacron has been a problem in our series of patients, and this problem has been noted by others. When an internal jugular vein is used, autogenous Drapanas shunts are well tolerated without thrombotic complications. In many patients at Moffitt Hospital in San Francisco, retroperitoneal renosplenal or adrenosplenal shunts are carried out; these procedures require considerable surgical expertise but have the advantage of being constructed outside the ascitic peritoneal cavity. Our experience with these shunts has been excellent.

What are the indications for portal-systemic shunts? In whom should they be used? In patients with documented varices, and in whom there has never been blood loss from varices, shunts should not be used. Although there is excellent evidence that variceal hemorrhage is avoided through the use of prophylactic shunts, decreased mortality from variceal hemorrhage in these cases is offset by the operative mortality and excess mortality from hepatocellular failure. Thus prophylactic portal-systemic shunts do not substantively improve long-term survival in patients with no blood loss from varices.[13,14]

Therapeutic portal-systemic shunts surgically created in patients who have had blood loss, or are having blood loss, from varices will arrest and prevent variceal hemorrhage. Recurrent variceal hemorrhage is unlikely in those patients in whom a technically adequate portal decompressive procedure has been carried out. However, when considering all patients with blood loss from varices, portal-systemic shunts will not improve long-term survival when compared with medical treatment.[15] In general, when therapeutic shunts are used, it appears that hepatic failure and operative mortality offset the improved mortality from hemorrhage that would be likely to accrue with patients having undergone successful portal decompression.[16]

A variety of factors have been examined to help predict outcomes of therapeutic decompression procedures and to select those patients likely to benefit from shunting. In spite of years of hemodynamic study, no predictive value has been documented in selecting patients or shunts on the basis of a variety of factors including portal blood flow, hepatic artery flow, hepatic artery/portal flow ratio, portal pressures or "maximum perfusion pressures."[17] A number of clinical factors, however, are associated with improved outcome (Table 6). We believe that Child's classification remains the most important determinant of outcome of surgical procedure (Table 7). Patients with a preoperative Child's classification of *A* or *B* have notably better chances of surviving surgical operation, and considerably better five-year and ten-year survival, compared with patients with Child's classification *C*.[18-20] Nonetheless, even in patients with Child's classification *C*, portal-systemic shunts, though they may not improve five-year survival, will prevent recurrent variceal hemorrhage. Our recommendations at San Francisco General Hospital are that in cases of Child's classification *A* or *B*, in patients with documented significant blood loss from varices (greater than 3,000 ml of blood transfusion), therapeutic portal-systemic decompression should be carried out when the patient's condition is hemodynamically stabilized. For patients with Child's classification *C*, in cases of acites, jaundice, malnourishment or encephalopathy, we recommend vasopressin therapy, blood transfusions and balloon tamponade to control hemorrhage. We do not advise surgical procedures for these patients unless all these other approaches

are unsuccessful in controlling blood loss or unless, with continued medical management, the patients improve neurologically and metabolically.

Variceal hemorrhage is common in our urban environment, especially in cases of chronic alcoholism. The medical management is temporizing at best; surgical therapy seems to improve long-term survival in only a few patients with good hepatocellular function. It appears that the best therapy is to prevent the most important cause of cirrhosis and portal hypertension in our society —alcohol abuse.

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Electrocoagulation: Making a Curable Cancer Incurable?

IT REALLY IS AMAZING to see how well these patients have done by the electrocoagulation technique, because the method really destroys all our principles of surgical therapy for cancer. For example, if the cancer is confined within the wall of the bowel then one electrodesiccates, goes through, the wall of the bowel into the fat and the fat protrudes, the natural boundary has been broken and, in a few instances, the patient then has repeated attacks of bleeding or of infections. And, a curable cancer has eventually been made incurable by the procedure.

—CLAUDE E. WELCH, MD, *Boston*

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Important Advances in Clinical Medicine

Epitomes of Progress — Ophthalmology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in ophthalmology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist the busy practitioner, student, research worker or scholar to stay abreast of these items of progress in ophthalmology which have recently achieved a substantial degree of authoritative acceptance, whether in his own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Ophthalmology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to: Division of Scientific and Educational Activities, California Medical Association, 731 Market St., San Francisco, CA 94103

Cryotherapy for Ocular Tumors

CRYOTHERAPY is effective in certain ocular tumors. It is sometimes preferable to excision for benign cutaneous disorders of the eyelids. such as keratoma, papilloma, verruca and keratoacanthoma. In the treatment of trichiasis, it has become the method of choice. Some benign angiomatous retinal tumors and certain small malignant retinoblastomas can also be managed by cryotherapy. In recent years, there has been considerable interest in its use for treatment of periocular basal cell carcinoma.

Although dermatologists have used cryotherapy for decades, there is controversy among opthalmologists regarding its role. This persists not only because it is a departure from the traditional surgical approach, but also because of the greater morbidity associated with periocular tumors.

Zacarian has reported a 2.2 percent recurrence of basal and squamous cell tumors treated by cryotherapy. However, an 8 percent recurrence was observed in periocular tumors. Those most likely to recur are sclerosing basal cell tumors and recurrent tumors. Involvement of the canthal region and conjunctival surface is particularly dangerous. In such instances, a histologically controlled excision is preferable. Many investigators report success in treating squamous cell carcinoma; however, meibomian gland carcinoma and melanoma should not be treated by cryotherapy.

Inability to obtain tissue confirmation of complete excision is partially compensated by monitoring tissue temperature to insure generation of an adequate cryogenic reaction. It is also important to use liquid nitrogen as the freezing agent to obtain the maximum possible freezing velocity. Repeated cycles of rapid freezing and

slow thawing to at least −30°C maximize tumor destruction.

The advantage of cryotherapy over all other methods is its simplicity. A single, inexpensive outpatient treatment is almost always sufficient. Freezing does not jeopardize the function or appearance of the eyelid, nor does it damage the lacrimal excretory ducts. Cryotherapy, surgical operation and radiation are all useful in treatment of periocular tumors. It is important to understand the advantages and limitation of each in selecting which modality to use. Best results can only be obtained with proper case selection and careful technique.

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Adenovirus Infections of the Eye

ADENOVIRUS INFECTIONS of the eye are a universal problem affecting the conjunctiva and frequently the cornea. They seldom cause serious permanent visual loss but do cause significant morbidity. Many adenovirus types sporadically infect the eye and types 3, 7, 8 and 19 have caused epidemics of keratoconjunctivitis.

Epidemic keratoconjunctivitis has been recognized since the turn of the century but became a problem in the continental United States during World War II with outbreaks of "shipyard conjunctivitis" in West Coast shipyards.

Type 8 keratoconjunctivitis illustrates the characteristic clinical appearance and course of ocular adenovirus infections. Photophobia, irritation and tearing begin abruptly, accompanied by an acute follicular conjunctivitis with occasional subconjunctival hemorrhages or pseudomembranes and frequent ipsilateral preauricular lymphadenopathy. The other eye is commonly, though less severely, infected in two to five days. The conjunctivitis resolves in two to three weeks, usually without scarring.

Vision is blurred and distorted in 50 percent of cases with corneal involvement (keratitis). Initially, the virus infects the corneal epithelium and about three weeks later typical subepithelial opacities, presumably an antibody response to the virus antigens, appear. These opacities usually clear in weeks to months though scars may persist, and occasionally there is a permanent visual loss. Corneal changes in types other than 8 and 19 are less severe and disappear more quickly.

Ocular adenovirus infections in children and type 3 infections often have associated systemic symptoms.

Diagnosis, usually clinical, is easy during an epidemic but more difficult in sporadic cases. It may take two to three weeks for a virus to grow in culture and for serum neutralizing antibody titers to rise. Direct immunofluorescence of conjunctival scrapings is a new, fast, accurate way of identifying the virus. However, these diagnostic tests require special laboratories.

Treatment of the keratoconjunctivitis is nonspecific. Uses of lubricants, astringents, cool compresses, mydriatics and antibiotics to prevent secondary infection are the mainstays of therapy. In rare cases, topical glucocorticoids are used to eliminate visually-incapacitating subepithelial infiltrates; however, it may be difficult to discontinue the administration of steroids, prolonging the course of the disease. Trifluridine inhibits replication of some adenovirus types to varying degrees in tissue culture, but there are no antiviral agents effective against adenovirus available for clinical use at present.

The recognition of possible ocular adenovirus infection and institution of appropriate measures to prevent its spread are crucial. Although the abrupt onset of redness, irritation, tearing, and photophobia unrelieved by astringents or antibiotics is often noninfectious, infection, including adenovirus, should be suspected. More than 95 percent of adults in the United States are susceptible to adenovirus type 8. The virus is spread by close contact and type 3 can be spread in swimming pools. Adenovirus has an incubation period of 5 to 12 days, is shed from the eye up to two week after the onset of symptoms, has been isolated from asymptomatic patients and survives in dried ocular secretions for a week at room temperature. Epidemics have been started in and sustained by eye care centers; adenovirus can be spread by an examiner's fingers or by infected equipment. Routine and careful washing of hands by examiners, especially after examining patients with red eyes, and cleaning diagnostic instruments after each use can prevent the spread of adenovirus. Affected staff, including physicians,

should not work for 10 to 14 days after symptoms begin. The attendent loss of income and the disruption of the practice can usually be prevented by routine care during eye examination.

We know adenovirus can cause keratoconjunctivitis. We can quickly identify it by direct immunofluorescent staining of conjunctival cells, and we can frequently prevent its spread. We are now awaiting the development of a specific antiadenovirus agent.

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HLA Antigens and Glaucoma

THE HISTOCOMPATIBILITY (HLA) SYSTEM is of immediate interest and relevance to many workers in ophthalmology. Research in this area is in an extremely active phase. Data are being collected and new information is becoming known; however, one has to be prepared for changes in views and ideas as a result of improved methods and investigations.

Associations between HLA antigens and a particular disease are characterized by relative increases in the frequency of particular antigens in the group of diseased patients as compared with racially and ethnically matched control groups. Thus, control is important as the normal frequency of certain HLA types varies considerably in various parts of the world. For example, HLA-B5 is found in 34 percent of Japanese and only 4 percent of Africans; HLA-B8 is found in 25 percent of British and 1 percent of Japanese control subjects.

Both ankylosing spondylitis and Reiter syndrome are associated with iridocyclitis and there is a statistically significant increased incidence of HLA-B27 in these systemic diseases.

Studies suggest a relationship between HLA types and recurrent corneal herpes simplex infections. Zimmerman's co-workers found that HLA-B5 was significantly increased in the group with recurrent herpes simplex virus keratitis as compared to the control group.

Inheritance of the HLA system was determined in 235 persons from 64 families with retinoblastoma and HLA antigens of 255 healthy blood donors was determined as a control group. They found an increase of HLA-BW5 antigens among the retinoblastoma patients, particularly among hereditary cases of retinoblastoma. Simultaneously, they report a decreased HLA-12 antigen frequency among both hereditary and nonhereditary retinoblastoma patients.

There is no significant deviation of any antigen which could be found in Eales disease, chorioretinitis or central serous retinopathy. However, in patients with malignant choroidal melanoma, there is a significantly higher incidence of HLA-AW32. HLA analysis in a total of 514 patients with malignant melanomas in other parts of the body failed to show any significant HLA deviation. Skepticisms are also enhanced by the fact that so far all disease-associated HLA antigens belong to the HLA-B or HLA-D locus, or both.

Aviner and co-workers reported an increased frequency of HLA-BW35 in primary open-angle glaucoma in a predominantly white patient population with a high percentage of patients of Jewish background. These authors warned that the increase was so low it might represent a chance deviation. A series of publications from Washington University in St. Louis found the frequency of B7 and B12 significantly increased in primary open-angle glaucoma.

However, Rich and associates, Dangmar and co-workers and others could show no correlation of any of the serologically studied HLA antigens with primary open-angle glaucoma.

Kass and associates from Washington University, St. Louis, enlarged their series, reviewed all their data and concluded that the associations between A and B loci of the HLA antigen system and primary open-angle glaucoma are less impressive than previously reported. At present, there is no clear-cut evidence of HLA antigens having a definite association with open-angle or angle-closure glaucoma.

In families in which there is a familial disease problem, sometimes an HLA link can be found. For example, all of the children in a family who have received their mother's HLA haplotypes will have her disease and the children that have another haplotype will be free of the disease. In this way, although a particular disease cannot be found to be linked to a particular HLA type by

general population studies, a disease can nevertheless be found to be tied in some way to the HLA complex. As the HLA story continues to unfold, we will learn more about these important antigens in ophthalmology.

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Automated Perimetry

AUTOMATED PERIMETRY, like computerized axial tomography (CAT scan), is one of the exciting newer developments from the computer age. Ophthalmologists for years have purchased numerous perimetric devices in an attempt to more efficiently evaluate visual field defects. Since 1975 we have had the opportunity at the University of California, Davis to help design and evaluate several of these automated perimeters. Our initial skepticism about automated perimetry has been replaced by genuine optimism. We are inclined to agree with Fankhauser and associates and Heijl and co-workers who found automated screening superior to conventional kinetic perimetry.

The ideal automated perimeter should offer several advantages over manual techniques and include the following features: (1) precise detection and assessment of visual field defects of all types with a negligible false alarm rate, (2) accurate monitoring of progressive visual field loss, (3) standardization of stimulus conditions in test procedures, (4) electronic monitoring of eye movement, (5) reduction in examination time, (6) administration of testing procedures by persons with minimal or no perimetric training and (7) reasonable purchase price.

Unfortunately, physicians have been inundated by a variety of first generation automated perimeters. Because decisions about treatment modalities are frequently based on perimetric data, we feel it is mandatory that these perimeters be validated by controlled clinical studies to assess whether they fulfill the criteria for an ideal automated perimeter. Without such controlled published data, a physician will not be able to make an intelligent decision as to which automated perimeter is appropriate for his or her practice. This is no small decision because automated perimeters can range in price from $4,000 to $100,000.

Most automated perimeters use a static or suprathreshold static program. Some devices have kinetic programs but the versatility of static programs is becoming evident. Goldmann kinetic perimetry is the well established standard. However, it is likely that when physicians become familiar with static testing, the advantages of static and suprathreshold static perimetry may well replace kinetic programs.

In summary, the usefulness of automated perimetry is a reality. When automated perimeters are properly used and their findings validated by controlled studies, they can be excellent detectors of visual field defects. The assessment of visual field defects is somewhat limited, however, by the automated perimeters available at present. Nonetheless, as newer generations of automated perimeters are developed, it actually may be possible to see a computerized three-dimensional view of the island of vision with scotomas scooped out of the island. In the future, there may be nothing about visual fields left to the imagination.

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Lasers in Ophthalmology

HISTORICALLY, ruby lasers were the first lasers used clinically in ophthalmology. A ruby laser utilizes the photostimulation of a ruby crystal to produce coherent red light. More recently, argon lasers have gained general acceptance over other visible spectrum laser systems. This type of laser utilizes electrical stimulation or argon gas to produce a coherent green beam that is dependent

on pigment (or blood) for absorption of energy. Most energy absorption occurs in the pigment epithelial layer of the retina. Either of these lasers can be used to surround a retinal tear to prophylactically prevent retinal detachment. The laser energy then forms a scar that effectively seals this tear. Laser photocoagulation cannot be used when significant fluid has accumulated between the sensory retina and pigment epithelium causing a frank rhegmatogenous (tear-induced) retinal detachment.

Ruby or argon laser retinal photocoagulation has now been proved to help in the control of proliferative diabetic retinopathy. The laser energy is used to treat specific areas of neovascularization as well as to reduce the overall metabolic needs of the retina in the form of panretinal ablative photocoagulation. Uses in photocoagulation of vascular tumors, central serous chorioretinopathy, sickle cell retinopathy, Coats disease and other proliferative retinopathies are other common applications of these laser systems. Although the ruby and argon laser systems have been used for treatment of macular degenerative disease and for some inflammatory diseases in the macular region, the results have been discouraging. Iridotomy by laser is another accepted anterior segment application of this form of energy.

Xenon arc photocoagulation, which was the first generally available method of retinal photocoagulation, is still used extensively but is technically not a laser and will not be considered here.

Diabetic maculopathy, a common cause of visual impairment in cases of diabetes mellitus, is undergoing a five-year national cooperative randomized study and the overall benefit of laser photocoagulation in this condition has not been determined. Panretinal photocoagulation also has recently been shown advantageous in the control of rubeosis iridis.

The adaptation of a carbon dioxide laser for intraocular use has been recently reported. This offers a unique method of cauterizing or cutting with infrared energy inside the eye at the time of vitrectomy. Some of the indications for the use of transvitreal carbon dioxide laser photocautery at the time of vitrectomy would appear to be retinal tears discovered at or induced by vitrectomy, fibrovascular fronds overlying the optic nerve or elsewhere that are actively bleeding, and rubeosis iridis that is actively bleeding and cannot be controlled. Clinical trials are currently in progress.

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Acute Angle-Closure Glaucoma

IN THE CLOSED angle type of glaucoma, the peripheral iris blocks the drainage system (trabecular meshwork) at the angle of the anterior chamber. Although angle-closure may be secondary to other ocular diseases, such as iritis, pupillary block is the most common cause. In this condition, the normal flow of aqueous humor through the pupil is partially blocked, causing the peripheral iris to billow forward, to contact the trabecular meshwork and thereby prevent aqueous drainage from the eye.

The process may be triggered in susceptible persons by pupillary dilation (either physiologic or pharmacologic), the prone position or, paradoxically, strong miotics. The blockage of the trabecular meshwork may occur suddenly or slowly, producing two different clinical features: acute or chronic angle-closure glaucoma. Intermittent (subacute) presentations also occur. When blockage occurs suddenly, the intraocular pressure rises rapidly and to high levels, causing pain in the trigeminal distribution with associated corneal edema. The latter results in blurred vision and colored halos around lights. Reflex vagal stimuation may lead to nausea, vomiting and even abdominal pain. Irreversible and severe optic nerve damage may occur within a few hours. The patient may describe previous episodes that spontaneously subsided.

Findings include conjunctival hyperemia, distorted corneal light reflex, shallow anterior chamber, fixed, middilated pupils and elevated intraocular pressure. Confirmation is by gonioscopy. Between attacks the intraocular pressure may be normal. When the diagnosis is in doubt, some

authorities advocate darkroom, dilation or prone provocative tests, but their value is controversial.

Immediate treatment is aimed at reducing the intraocular pressure with intravenous administration of acetazolamide and a hyperosmotic agent such as mannitol or glycerin while concurrently pulling the iris away from the angle with topical 2 percent solution of pilocarpine. Definitive therapy consists of peripheral iridectomy which deflates the billowing iris. Classically, this has been done surgically with excellent safety and effectiveness. Recently, lasers have been used by some to produce a hole in the iris. This is not always successful but theoretically is safer. Postoperatively, supplemental use of antiglaucoma medication may be necessary if permanent damage has occurred to the outflow system. Prophylactic iridectomy is advocated by many for the other eye because the disease is usually bilateral.

This rare disease is frequently misdiagnosed. Since complete cure may be obtained if caught in time, early diagnosis is mandatory.

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Automated Refraction

CLINICAL REFRACTION is that part of the opthalmologic examination concerned with the diagnosis and treatment of refractive errors. Automated refraction aims to expedite this by instruments requiring minimal operator skill and minimal patient cooperation. Such instruments may be objective or subjective.

Objective refractors measure dioptric status of the eye independent of patient responses. The patient is only required to stay reasonably still and look at a distant fixation target or its equivalent. The earliest and occasionally still useful objective instrument is the ophthalmoscope. The conventional clinical instrument is the retinoscope. Advances in electronics and microcomputers have made possible devices using infrared light and image analysis which reduce measuring time to a matter of seconds. A calibration bias is built into the instrument to compensate for chromatic aberration, and intermittent or automatic blurring (fogging) inhibit instrument accommodation. Poor patient cooperation and cloudy ocular media limit accuracy. Most 5-year-old children can be examined, and overrefraction for aphakia and contact lens fitting is possible. A warning signal or blank printout indicates instrumental difficulties. Currently available commercial automated instruments are the 6,600 Auto-Refractor (Acuity Systems, Inc.) and the Dioptron II (Coherent, Inc.). Electrophysiologic techniques using visual evoked potentials to measure refraction are in the research stage.

Subjective refractors are partially automated devices based on the optometer principle using innovative lens systems and targets to overcome instrument accommodation and facilitate subjective discrimination. Computers expedite target sequences and recordng. Total time depends on how many tests are done and ranges from 5 to 20 minutes per patient. Greater operator skill and more patient cooperation are required than with objective devices. Inadequate measurements are confirmed by poor acuity. Two currently available commercial subjective refractors are the SR-III (American Optical Co.) and the Vision Analyzer (Humphrey Instruments, Inc.). Laser and other computerized refracting systems are in developmental stages.

All automated refractors are designed to be operated by technicians after "a few hours training." Objective instruments do not tell what the patient sees, how he sees, or even if he has seen; a perfectly valid but useless reading can be obtained on a blind eye. The experienced clinician, therefore, seldom prescribes from objective measurements if he has the option of confirming results subjectively. Accuracy equals but does not exceed competent retinoscopy—the only procedure objective refractors replace. Subjective refractors conserve space and time but may not allow for evaluation of presbyopia, binocular motility, and accommodative anomalies, often an integral part of clinical refraction. Accuracy of subjective instruments is comparable to standard subjective tests. Precise correlations are not possible since different corrections may give equal acuity. In all cases, the final prescription for spectacles, if any, depends on symptomology as well as machinery.

The chief advantages of automated refractors, aside from participating in the seemingly headlong rush to computerize everything in sight, are to provide convenient rapid measurements requir-

ing limited patient cooperation. This is particularly useful in children and illiterates, and in mass screening programs. It also provides a measure of comfort to those who consider routine refractions a drudge. How much patient contact time should be delegated to nonprofessionals in the interest of efficiency is another problem.

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EDITORIALS

Physician Compliance

IN THE JARGON of quality assurance we speak frequently of patient compliance but not often of physician compliance. By patient compliance we mean the extent to which patients comply with the treatment recommended, presumably with their own informed consent. Physician compliance is a term not frequently used (if at all), but would imply the extent to which the physicians might comply with therapeutic recommendations which are based on presumably sound scientific evidence. Data are accumulating that show patient compliance is often less than physicians might expect. However, what is not so well documented is that physician compliance may often be less than what patients or anyone else might expect. Too little is known of the reasons for these phenomena.

The observations reported elsewhere in this issue by Pien and co-workers give one pause. We like to think that there is a substantial amount of firm data and good experience upon which to base the indications for the selection and use of antibiotics in everyday hospital practice. We would also like to think that a careful regimen of chart reviews, educational programs for physicians and a ready availability of expert professional consultation should bring about a close correlation between what ought to be and what is. Yet such is not always the case as their observations in a community hospital so clearly attest. Why?

One can only assume that there must be other factors at work which are as yet only poorly understood. Some might say that the doctors involved are somehow at fault for not hearing even though they may have been listening, or for not using the readily available consultation more often. But this seems a simplistic answer. It seems more likely that physicians rely more heavily on their own practice experience and that of their immediate associates than is generally assumed. Also physicians are trained and learn to be critical of what they hear and are told, whether by patients or professional experts, until they are convinced it makes sense to them clinically. And most physicians have lived long enough to know that what is scientifically espoused as truth today may not be truth tomorrow—something the general public is also beginning to discover. In short it may be that many if not most physicians are unlikely to change their practice behavior unless in their own experience they are convinced that the need to change is real and that it will make a significant difference to them or to their patients.

It would seem that similar factors may also be at play in the matter of patient compliance. Patients are becoming more and more critical of what they are told, more and more aware that physicians and medical sciences are not infallible, and it is reasonable to think they would be more apt to comply with treatment that seems to make sense to them and likely to make a difference commensurate with its cost and inconvenience.

As stated previously the issues and forces at work here are far from being well understood. Until they are, the fact that both physician and patient will each do as he or she thinks best in a given circumstance needs to be fully recognized, even if not fully condoned.

—MSMW

Immunity in Diabetes Mellitus: Impaired or Enhanced?

THE ACUTE INFLAMMATORY RESPONSE to invasion of the body by pathogenic microorganisms is critical as a determinant of the outcome of infection. Several studies have shown that phagocytes must arrive at the site of invasion within a brief period (two to four hours) if infection is to be suppressed or contained. Normal persons certainly have no trouble in preventing or confining the numerous

microbial intrusions of the body which must occur every day. In contrast, a person with an inherited or acquired defect in antibody production, complement activity, phagocyte function or cell-mediated immunity usually suffers severe and repeated infections. In addition to these two extremes on the scale of immune competence, however, there are a number of persons with diseases not associated with profound immunodeficiencies who seem to have an increased incidence or severity of infectious complications. These include persons with such diverse diseases as alcoholism and cirrhosis,[1] rheumatoid arthritis,[2] atopy,[3,4] and diabetes mellitus.[5-7]

As pointed out by Dr. David Tillman in the Specialty Conference on infection and diabetes mellitus published in this issue, there is considerable controversy about whether persons with the disease have an increased incidence of infections. It does appear, however, that certain types of infections—such as pyelonephritis, tuberculosis, mucocutaneous candidiasis, mucomycosis, osteomyelitis and malignant external otitis—occur more frequently in diabetic persons and are often more severe. A number of nonimmunologic factors could account for this. Thus, pyelonephritis is unlikely to be due to a defect in the host defense mechanism. I have yet to find urinary tract infections to be a major problem in patients with inherited or acquired defects in their immune system. Most assuredly, such infections are the results of *plumbing* problems secondary to the development of a neurogenic bladder or perhaps to high urine glucose concentrations. Cutaneous infections in persons with diabetes mellitus have been explained by pointing out that vascular insufficiency leads to poor perfusion, decreased inflammatory infiltrates, and difficulty in preventing or confining infection. There is no question that vascular insufficiency contributes to the problems observed in persons with the disease. One must not complacently accept simple explanations of observed phenomena, however. Such an approach would have certainly left undetected the underlying phagocyte abnormality in some patients with severe atopic eczema[3] or with severe burns[8] because infections could be expected to develop when normal skin barriers were no longer intact. Vascular insufficiency alone, therefore, cannot explain all of the infectious complications in patients with diabetes mellitus.

A number of investigators have chosen to examine the host defense mechanism in the disease but, unfortunately, many of these studies have yielded conflicting results. It is likely that the differences observed result from different methodologies and from the lack of a homogeneous study population. Moreover, any number of metabolic and hormonal factors have now been shown to affect leukocyte function and the host defense mechanism: insulin, adrenergic agents, prostaglandins, steroids and even glucose levels have been shown to profoundly affect polymorphonuclear leukocyte (PMN), macrophage and lymphocyte function.[5-7,9-11] With all of these agents having direct and profound effects on the host defense mechanism, it is easy to see why studies should yield conflicting data. It is likely, therefore, that investigators interested in the effects of diseases such as diabetes on the host defense mechanism will have to compare function in the same person over a period of time during wide variations in disease activity or control. A profound and persistent defect, such as that seen in the inherited immune deficiency diseases, will often not be detectable in these subjects. Rather, abnormalities will likely be present during the height of metabolic or physiologic derangement during or before the development of infection.

Dr. Miller has pointed out the most consistent defect observed in diabetic patients is one in PMN chemotactic responsiveness. The incidence and severity of this abnormality has varied from study to study. Drs. Miller and Baker[6] found depression of PMN chemotaxis in each of ten patients with juvenile diabetes. Mowat and Baum[7] reported in the *New England Journal of Medicine* that adults with the disease also have a defect in PMN chemotaxis. When one studies their data carefully, however, it becomes apparent that only five of 21 patients had chemotactic indices that were one standard deviation or more below the average mean of controls and none had levels below two standard deviations from the mean. In our studies, we found that approximately a third of young patients with diabetes had chemotactic activity significantly below (2 SD) that of controls.[5] Moreover, none of the patients had chemotactic depression like that seen in patients with severe abscess formation.[3] The defect, therefore, does not appear to be a particularly severe one and not all persons with diabetes mellitus have it. The infections that some persons with the disease do have—such as mucocutaneous candidiasis, occasional abscess formation or infected ulcers—are not incompatible with those suffered

by patients with underlying PMN abnormalities.[3,4,8] Consequently, the observed abnormality may have functional significance. As mentioned, adhesion also seems to be affected in diabetes and this could contribute to the problems observed. I am less convinced of the significance of the described phagocytic or killing abnormalities because, in general, the methodologies employed have left something to be desired and the magnitude of the defect has not been great (73 percent of control in reference 12; 77 percent of control in reference 13).

Dr. Pitchon has reviewed the studies on lymphocyte responsiveness in diabetes which suggest that mitogenesis is depressed only during poor metabolic control. Both increased glucose and fatty acid concentrations depress PHA transformation *in vitro,* which may aid in explaining this finding. At any rate, the available data do not indicate a consistent, inherent defect in diabetic lymphocyte function.

With these possible *defects* in mind, what evidence do we have that some immune values in diabetes may be enhanced? Of great recent interest have been reports of islet cell antibodies or cell mediated immunity to pancreatic extracts in patients with diabetes mellitus.[14-16] Such hyperreactivity may only be a secondary phenomenon resulting from previous insult to the islet cell leading to damage and release of altered antigenic components. Alternatively, this may be a primary response or one elicited by an occult infection which leads to the diabetic state. Such immune hyperreactivity appears to be linked to HLA types as reported in juvenile diabetes mellitus.[17] In addition to islet cell antibodies, high levels of circulating anti-insulin antibodies often form. This is of particular interest in view of Dr. Miller's findings which suggest that chemotactic dysfunction does not appear until after insulin therapy. If some portions of the immune system are enhanced in diabetes mellitus, how could this result in the deficiencies observed?

Circulating immune complexes have been observed in the sera of a number of persons with the disease;[18] moreover, renal tissue specimens show fine granular deposits on basement membranes which contain IgG, IgM and components of complement. Therefore, circulating immune complexes containing islet cell antigens or insulin may be present in the plasma of diabetic patients. Such antigen-antibody complexes could, at least partially, trigger the complement system resulting in a subsequent decrease in the ability to generate chemotactic factors in diabetic sera as observed by Dr. Miller. Moreover, the *in vivo* generation of complement derived chemoattractants by antigen-antibody complexes could deactivate the PMN to other chemoattractants resulting in the PMN defect observed. This has been reported in patients with nephritis with circulating immune complexes.[19] Both the cellular and humoral defects in chemotaxis, therefore, might be explained on the basis of circulating antigen-antibody complexes resulting from the initial hyperreactivity of the immune system in diabetes mellitus.

Diabetes mellitus may well be a paradox of increased and decreased immune reactivity: one resulting in, or contributing to, the development of the diabetic state; the other resulting in severe or perhaps more frequent infections. It appears likely, however, that we are dealing with another major illness and many of its complications that can be attributed to faulty regulation of the immune system.

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Violet Is Not Always Beautiful

IODINE and the thyroid gland have been inextricably linked since the discovery of the former during the French military expansion of the early 19th century. Napoleon's ambitions had set France at war with almost all her neighbors simultaneously. Blockaded at sea by the British navy and on land by the armies of Prussia and Austria, France found that the supply of chemicals necessary for the manufacture of gunpowder was cut off. The Emperor set his scientists to manufacture saltpeter artificially in special "nitre plantations." One of the steps involved extracting soda from ashes of seaweed in large metal vats. The vats were cleaned periodically with hot acid. Observing this process one day in 1811, Bernard Courtois was astonished to see, arising from the muck, intensely beautiful violet-colored vapors which deposited lustrous metal-like crystals on the cooler parts of the vessel. Samples were sent to the distinguished French chemist Gay-Lussac, who named the material *iode,* derived from the Greek word meaning violet colored. Some of this material came immediately into the enemy hands of Sir Humprey Davy, who proved that it was an element and anglicized its name to iodine.

Eight years after Courtois' discovery, Andrew Fyfe, a lecturer in chemistry at the University of Edinburgh, found that common sea sponges also contained large quantities of iodine. Shortly thereafter, Jean-François Coindet, a prominent Swiss physician who commonly treated his many goitrous patients in Geneva with the centuries-old remedies of burnt sponge or seaweed, suspected that the violet crystals might be the active ingredient common to these two substances. He reported the great success of his therapeutic trial of the new element in 1820 and the use of iodine rapidly spread throughout the Western world, much as cortisone did more than a century later. This new miracle substance was prescribed for every conceivable condition ranging from chilblains and dropsy through scrofula and syphilis. From the initial publication of tincture of iodine in an 1821 pharmacopoeia by François Magendie, 1,700 approved names of iodine-containing substances were listed by 1956.

Since burnt sponge and seaweed had been administered topically as well as taken orally, the methods of applying iodine during the 19th century were scarcely less numerous than the variety of preparations available. It was given as a vapor, in baths, in pills, in candy, by irrigation, in cigarettes, in soaps, in hair tonics, and as a contraceptive. In French hospitals it was common practice to hang strips of gauze saturated with iodoform from the ceiling like flypaper. Even the laity were so impressed with this new gift from the collaboration of Science and Heaven that they carried little bottles of iodine hung round their necks like amulets to ward off disease. In Geneva it was said that the iodine dropping-bottle replaced the bonbonniere as the centerpiece of social gatherings in the evening salons.

The first specific reference to the use of tincture of iodine in wounds was by the English surgeon John Davies in 1839. It was widely used in the treatment of battle injuries during the American Civil War and World War I, but rapidly lost favor as a first line of antibacterial defense when the more efficacious and less necrotizing antibiotics came on the scene during World War II. Nevertheless, it is still widely employed for its antibacterial properties.

Iodine and the Thyroid Gland

Getting back to the relation of iodine to the thyroid gland, at the time Coindet initiated his therapeutic trial, the fact that the thyroid contained iodine was as unknown as was the purpose for which God set this strange organ in the neck. In spite of this ignorance, a number of important studies and theories appeared during the 19th century. In 1831 Jean-Baptiste Boussingault, a mining engineer with protean talents, discovered during a sojourn in Colombia—a region with unevenly distributed severe endemic goiter—that the natives who used salt from certain natural deposits had less goiter than those taking salt from elsewhere. He found that the iodine content of the salt used by the different groups was in-

versely correlated with the prevalence of thyroid enlargement and suggested that providing iodized salt would be a useful prophylactic measure against goiter. During the mid-19th century another French chemist, Gaspard Adolphe Chatin, found that there was a general deficiency of iodine in the water, soil and vegetables in areas with a high incidence of goiter.

However, the French Connection was not widely accepted. Iodine was often given in excessive doses and produced serious reactions in some persons. Its use in the treatment of many diseases, including goiter, was therefore gradually abandoned. In fact, in 1821, one year after his initial earthshaking discovery, Coindet warned that in certain goitrous patients treated with iodine, toxic symptoms including accelerated pulse, palpitation, increased appetite, rapid emaciation, insomnia and muscular weakness developed. He was the first, therefore, to describe thyrotoxicosis, several years before the publications of Graves or Basedow. It has even been suggested that the appropriate eponymic designation of spontaneous hyperthyroidism should be "non-iodide-induced Coindet's disease." Vagenakis and co-workers have recently shown that Coindet disease can also be induced by administration of large doses of iodide to patients with nontoxic goiter living in iodine-sufficient regions.

Toward the end of the 19th century, basic and clinical studies established that the thyroid contained a substance whose absence resulted in myxedema. Shortly after the discovery that orally administered thyroid substance was effective in treating myxedema it was found that ingestion of thyroid also caused a remarkable diminution in the size of nontoxic goiters. It was an attempt to find the active principle in the thyroid gland that caused goiters to shrink, not to identify the principle that was effective in treating myxedema (since myxedema was a much less common disorder than goiter), that eventually led German pharmaceutical chemist Eugen Baumann to the discovery in 1895 that iodine is an invariable constituent of the normal thyroid gland.

During the 20th century knowledge of the importance of iodine to thyroid physiology and disease has become increasingly sophisticated, albeit incomplete. David Marine revitalized the iodine-deficiency theory of endemic goiter and persuaded the school board of Akron, Ohio, to institute the first large-scale clinical trial to prove the efficacy of iodine-supplementation in preventing endemic goiter in children in 1917. Shortly thereafter, Plummer began preventing postthyroidectomy storm in thyrotoxicosis by preoperative treatment with Lugol's solution. Isolation of thyroxine by Kendall was followed by determination of its structure by Harington. The considerably more potent triiodothyronine was identified by Gross and Pitt-Rivers in both the thyroid and plasma in 1952. The extrathyroidal conversion of thyroxine to triiodothyronine and the intricate metabolism of thyroid hormones are currently under active investigation in a number of laboratories.

Hypothyroidism

Isolated reports of hypothyroidism induced by iodide therapy were followed by the demonstration by Wolff and Chaikoff in 1948 that administration of large doses of iodide to rats would transiently inhibit thyroid hormone formation for one to two days, although the inhibitory effect of iodide disappeared thereafter despite maintenance of high plasma levels of inorganic iodide. Raben proved that the Wolff-Chaikoff effect was due to a high intrathyroidal concentration of inorganic iodide; Braverman and Ingbar subsequently found that dissipation of the Wolff-Chaikoff effect was correlated with a decrease in the capacity of the thyroid iodide pump to maintain a high thyroid/plasma iodide gradient. This adaptive decrease in iodide pump activity to high concentrations of plasma iodide provided a plausible explanation for the infrequency with which iodide-induced myxedema or goiter is seen in spite of the widespread use of large doses of iodide in the treatment of chronic pulmonary and other diseases. Apparently, only patients with inherited autoregulatory defects or those with thyroids damaged by disease or surgical procedures (chronic thyroiditis, subtotal thyroidectomy, radioiodine therapy and the like) have this adaptation deficiency. The amelioration of thyrotoxicosis by large doses of iodide is not due to the Wolff-Chaikoff effect, but is due to a separate, poorly understood, action of high concentrations of intrathyroidal iodide to reduce thyroid secretion in very active glands.

The case reported by Prager and Gardner in this issue of the journal of an unusual occurrence of goitrous hypothyroidism apparently due to topical absorption of iodine chronically applied to a perineal fistula points out the ability of iodine to be absorbed from portions of the body other than the gastrointestinal tract and that organic,

as well as inorganic, iodine can produce the Wolff-Chaikoff effect after metabolic deiodination. Unfortunately, the possibility that their patient may have had chronic lymphocytic thyroiditis or some other non-iodide-related form of goitrous hypothyroidism is not excluded with certainty. The plasma inorganic iodide level obtained at a time when the patient was still being treated with iodine packing (although measured after storage for several months) was only three times greater than normal. The prompt regression of the patient's goiter with thyroxine therapy and the absence of antithyroglobulin and antithyroid microsomal antibodies do not exclude a diagnosis of chronic lymphocytic thyroiditis, contrary to the suggestion of the authors. Hypothyroidism from chronic thyroiditis is not always permanent and a spontaneous return to euthyroidism or even progression to thyrotoxicosis has occasionally been reported. More convincing validation would have been to show that readministration of high doses of iodide (either orally or topically) would produce a long-lasting block in thyroid hormone formation, but such confirmation would not be obtained easily.

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Natural Salicylate Foods

I DO THINK that we have underestimated the use of various kinds of foods for specific things. There are an awful lot of people who take large amounts of aspirin . . . much to the distress of their stomach linings. There are a whole host of [high-content] salicylate foods, and among these are potatoes, most of the fruits, apricots, almonds. . . . By utilizing some of these, one can reduce the need for exogenous medications. If you take four almonds, it will have enough salicylate for one 5-gram aspirin tablet. There are some of these nutritional applications that we have not utilized.

—IVAN E. DANHOF, MD, *Dallas*

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CASE REPORTS

Refer to: Prager EM, Gardner RE: Iatrogenic hypothyroidism from topical iodine-containing medications. West J Med 130: 553-555, Jun 1979

Iatrogenic Hypothyroidism From Topical Iodine-Containing Medications

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DEVELOPMENT OF HYPOTHYROIDISM with and without goiter is known to occur in certain persons following prolonged administration of excess iodine.[1-3] Such inhibition of thyroid hormone synthesis has generally been reported following ingestion of excess iodine in the form of iodide. However, organic compounds containing iodine, particularly in a labile form, are also capable of producing this effect.[4] We report here an instance in which two topical iodine-containing medications, iodoform and povidone-iodine, used to cleanse an open wound for almost two years, led to the development of hypothyroidism with a slight goiter. To our knowledge this is the first time iodine in noningested, noninjected form has been implicated in the induction of hypothyroidism.

Report of a Case

In a 26-year-old woman subtotal colectomy with ileostomy was carried out in 1972 and proctosigmoidectomy was done in 1973 because of ulcerative colitis with large pseudopolyps. During the second operation some remaining colonic tissue was found adhered to the vagina. Detachment of this tissue resulted in a small vaginal hole which connected through a lateral tract to a fistular tract existing where the rectum had been. In this situation serous-sanguinous drainage and menses had two exits.

Because the fistula did not close and the vagina did not heal, we undertook corrective surgical operation in 1974. A large abscess was discovered at the top of the fistular tract and was drained; the vaginal defect was also closed, but this repair failed. Following this operation, the perineal fistula was packed three times a week with a plain nonadhering strip (Adaptic, Johnson & Johnson) to prevent closure from the outside before the tract could fill in. Within several months the fistula greatly decreased in size, becoming about 10 cm long and 1 cm in diameter, with the connection to the vagina being about 0.5 cm in diameter and approximately 6 cm from the outside of the body.

In 1975, in an attempt to keep the fistula cleaner and thereby to accelerate healing, we changed our method of packing the tract. Three times a week we swabbed it out with povidone-iodine* (Betadine Surgical Scrub,† The Purdue Frederick Company), followed by packing with a short strip (25 to 30 cm) of 1.3-cm iodoform-impregnated packing (Nu Gauze, Johnson & Johnson).

After about 22 months of this regimen there developed in the patient (now 31 years old) distinct clinical signs of hypothyroidism, which was clearly shown in June 1977 by laboratory measurement of serum T_4 (thyroxine) levels: 2.3 μg per dl (normal, 4.5 to 13.0 μg per dl). A serum sample coincidentally available from February 1977 still contained normal amounts of T_4 (8.1 μg per dl). At the time the diagnosis of hypothyroidism was made, the patient's thyroid was firm and diffusely enlarged to roughly 2½ times normal size. A thyroid-stimulating hormone (TSH)

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*Povidone-iodine = polyvinylpyrrolidone-iodine = PVP-1.

†Betadine Surgical Scrub was used, unknowingly, although Betadine Solution, free of detergents, should be used for wound care.

TABLE 1.—*Iodine Exposure: Sources and Amounts*

Substance	Amount (Percent) and Form of Iodine Present*	Iodine Exposure: Amount of Substance Used (mg)	Iodine Exposure: Amount of Iodine (mg)	Iodine Exposure: Multiple of Recommended Daily Dose†
Table salt	0.01, KI	4,000	0.3	1.5
Povidone-iodine	0.75, available I	200‡	1.5	7.5
Iodoform packing	5.0, CHI_3	400§	20.0	100.0
TOTAL	....	....	21.8	109.0

*The entries for povidone-iodine and iodoform packing are based on personal communications from N. Healy, The Purdue Frederick Company, and H. L. Dickstein, Johnson & Johnson, respectively.

†A value of 0.2 mg was used as the recommended daily dose.

‡It was estimated that 0.2 ml remained within the body after swabbing out the tract.

§Determined by weighing a typical packing strip.

level of 64 μU per ml (normal, less than 10 μU per ml) confirmed primary hypothyroidism.

The patient was immediately placed on a regimen of thyroxine (50 μg per day, increasing gradually over one month to 150 μg per day) to ameliorate the clinical symptoms quickly. Simultaneously we discontinued application of both iodine-containing medications. The perineal fistula was subsequently managed with plain packing and later also with water jet lavage.[5]

We initially entertained a diagnosis of Hashimoto thyroiditis, especially in view of the patient's history of ulcerative colitis, an autoimmune disorder. However, two observations ruled out this possibility: the absence of abnormal levels of both antithyroglobulin and antimicrosomal antibodies and the disappearance of the patient's goiter within only one month after thyroxine therapy was begun.

We calculated the patient's exposure to iodine from all sources as shown in Table 1. It was found that three days per week the patient was exposed to almost 22 mg, or more than 100 times the recommended daily dose, and that 90 percent of this iodine came from the iodoform packing strip. Iodine can be absorbed systemically from povidone-iodine used in surgical practice,[6-8] and it is most probable that the iodine from iodoform is similarly absorbed. We believe the patient actually absorbed a significant amount of iodine through this wound because the strip, when removed, appeared by color and smell to be relatively free of iodine and because drainage from the fistula was minimal. Conservatively we estimate that, apportioned on a daily basis, the patient absorbed 4 mg of iodine out of a theoretical maximum of 9 to 10 mg per day. Lesser amounts have had an inhibitory effect on organic binding of iodine in persons with a history of iodide goiter and hypothyroidism.[9]

Since transient, reversible hypothyroidism due to excess iodine now seemed a good possibility, we completely stopped thyroxine therapy nine months later. The patient remained clinically and chemically euthyroid. Six weeks after cessation of medication the T_4 level was 8.7 μg per dl and the TSH level was 2.6 IU per ml (normal, 1.9 to 5.4 IU per ml). The patient's thyroid, which had been very small during thyroxine suppressive therapy, regained its normal size and remained soft.

Exposure to any chemical agent besides iodine could be readily ruled out as a cause of the hypothyroidism in this case. Acute (subacute) nonsuppurative thyroiditis was another possibility considered to explain the transient nature of the thyroid dysfunction, but since the pattern of clinical symptoms was inconsistent with that characteristic of such thyroiditis, we think this possibility unlikely.

During preparation of this report we measured the inorganic iodide present in the February 1977 serum sample (the only material still available) in an attempt to show absorption of excess iodine directly.*

The inorganic iodide level was 3.0 μg per dl (normal, not more than 1.0 μg per dl in the absence of excess dietary iodine consumption; frequently in the range of 0.2 to 0.5 μg per dl). The protein-bound iodine (PBI) level was 4.5 μg per dl (normal, 4.0 to 8.0 μg per dl), yielding a total serum iodine level of 7.5 μg per dl. However, by the time this analysis was done, the serum sample had been stored for 20 months at −16°C and had undergone four deliberate freeze-thaw cycles. In that time and under such conditions some decomposition of the PBI is expected to have occurred, with a consequent increase in the level of inorganic iodide. We suspect, therefore, that this serum sample, when fresh, contained less than 3.0 μg of inorganic iodide per dl. Though there is no way of knowing with certainty how much of the initial PBI was assayed as inorganic iodide, we estimate on the basis of the T_4 level of this sample (8.1 μg per dl) that the PBI should have been about 5.3 μg per dl rather than 4.5 μg per

*R. L. Gambardella, T. S. LaGanga, J. C. Sparks, and I. P. Sugar of Bio-Science Laboratories provided information and advice concerning analysis of the 20-month-old serum sample for inorganic iodide and protein-bound iodine.

dl. This adjusted PBI value would lead to an inorganic iodide level of 2.2 μg per dl, still clearly above normal. Conversely, adsorption of iodine to the walls of the storage vessel over time could have led to a decrease in the measured values of inorganic iodide and PBI.

The results of the analysis of the February 1977 serum sample, consequently, were consistent with the clinical evidence indicating that excess iodine was absorbed systemically.

Discussion

Many patients have taken large amounts of iodide, often more than 100 mg per day,[10] for respiratory ailments for long periods without adverse effect on the thyroid.[1-3] However, a few persons fail to adapt to high levels of iodine. Though the frequency of occurrence of this effect in the population is very low, enough cases of iodide goiter and hypothyroidism have by now been reported for this phenomenon to be generally known.[1,2,9] In a person predisposed to iodine-induced goiter and hypothyroidism some abnormality of the thyroid probably exists which prevents the usual adaptation to high iodine levels,[1,2] but this abnormality need never manifest itself in any thyroid dysfunction throughout the person's lifetime unless he happens coincidentally to be exposed over a prolonged period to excess doses of iodine.

Here we have reported the development of hypothyroidism with diffuse goiter in a patient exposed to excess amounts of iodine (about 4 mg per day) from iodoform and povidone-iodine used topically for about two years. That iodine in topical form has not been reported previously as a cause of hypothyroidism or goiter is undoubtedly due to the simultaneous occurrence of two rare events: susceptibility to inhibition of thyroid hormone synthesis by excess iodine and prolonged treatment of an open wound with iodine containing medications.

Povidone-iodine, however, has already been reported to induce the Wolff-Chaikoff effect, which involves transient inhibition of thyroid hormone synthesis by excess iodine.[11] Iodide goiter and hypothyroidism are actually the result of the failure to escape from the Wolff-Chaikoff effect in the continued presence of high iodine levels.[1] Therefore, any substance capable of inducing the Wolff-Chaikoff effect has the potential to cause goiter and hypothyroidism in some persons.

In view of the observations described here and in view of the increasing popularity of iodine-containing antiseptics, we urge physicans using any iodine therapy for a long time, even locally on wounds, to be alert to any change in function or appearance of the patient's thyroid gland. Furthermore, we caution against uncritical acceptance of a diagnosis of Hashimoto thyroiditis or idiopathic hypothyroidism without reasonable confirmatory laboratory evidence and without a reasonable search for agents, whether chemical or biological, that may have induced transient, reversible hypothyroidism in a particular person.

Summary

Hypothyroidism developed in a 31-year-old woman following 22 months of treatment of an unhealed perineal fistula with iodoform-impregnated packing strips and povidone-iodine solution. Use of these topical iodine-containing medications was discontinued and the patient placed on a regimen of thyroxine. Nine months later the thyroxine administration was stopped, and the patient promptly regained normal thyroid function. Induction of reversible hypothyroidism under these circumstances could be attributed to prolonged administration of excess iodine, which in rare persons leads to goiter or hypothyroidism, or both. The novel feature of this report is that iodine in topical rather than ingested or injected form was found to be the cause of the thyroid dysfunction.

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Refer to: Rau J, Ruskin J: Campylobacter fetus gastroenteritis. West J Med 130:556-558, Jun 1979

Campylobacter fetus Gastroenteritis

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IN THIS JOURNAL in 1974 Franklin and Ulmer discussed the protean clinical manifestations of Campylobacter fetus (formerly called Vibrio fetus) infection in man.[1] These included bacteremia, endocarditis, pericarditis, dysentery, thrombophlebitis, lung abscess, septic arthritis and meningitis. Spontaneous peritonitis[2] and salpingitis[3] have since been reported. Of all these entities, dysentery merits particular attention today because it may well be the most common and yet most overlooked expression of infection with this organism. This paper describes a case of gastroenteritis due to C. fetus and reviews studies from around the world that attest to an increasingly important role for Campylobacter as enteropathogenic bacteria.

Report of a Case

An 82-year-old white woman was well until three days before admission when she noted the abrupt onset of fever, midabdominal pain, vomiting and severe watery diarrhea. She said she had not eaten any raw meat or poultry or drunk unpasteurized milk, she had had no contact with animals or with people known to have a similar illness, and she had not recently traveled outside the Los Angeles area.

On physical examination the following findings were noted: blood pressure, 130/70 mm of mercury; pulse rate, 90 beats per minute; temperature 39°C (102.2°F), and respirations, 24. The patient appeared moderately ill. Except for minimal diffuse abdominal tenderness, no other abnormalities were found on physical examination.

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Admitting laboratory data included a leukocyte count of 8,500 with 26 percent neutrophils, 45 percent bands, 1 percent metamyelocytes, 22 percent lymphocytes, and 6 percent monocytes. The hemoglobin level was 15 grams per dl and the platelets were qualitatively normal by estimation. Other values were as follows: sodium, 139 mEq per liter; potassium, 3.1 mEq per liter; chloride, 98 mEq per liter; bicarbonate, 25 mEq per liter; blood urea nitrogen, 25 mg per dl; creatinine, 0.7 mg per dl, and random blood glucose, 135 mg per dl. Results of amylase and liver function tests were normal with the exception of a serum glutamic oxaloacetic transaminase level of 52 units (upper limit, 30 units). No abnormalities were shown on analysis of a urine specimen and the culture was sterile. A wet mount of a stool specimen showed a few polymorphonuclear cells per high-power field.

A diagnosis of bacterial gastroenteritis was made and the patient was treated with ampicillin and gentamicin given intravenously. She became afebrile in 12 hours and the diarrhea resolved after three days. Tests of stool specimens for ova and parasites as well as a culture for salmonella and shigella were negative. Administration of antibiotics was stopped after four days, and two days later the patient was discharged. On the day of discharge the bacteriology laboratory reported that all three cultures of blood specimens drawn on admission were positive. Gram stains of the broth showed curved Gram-negative rods that were consistent morphologically with a Vibrio species. Because we suspected that this might be a Campylobacter organism, the patient was given an additional one week regimen of doxycycline, 100 mg twice a day, to lessen the probability that the infection would relapse. She was examined again two weeks later and was well. At that time an upper gastrointestinal series and barium enema study showed no mucosal abnormalities.

The bacteremic isolate was identified as C. fetus, subspecies jejuni because of the following characteristics: it grew on blood agar and chocolate agar in an atmosphere of 5 percent to 10 percent carbon dioxide at 42°C. It also grew in 1 percent glycine agar. It was oxidase and catalase positive, reduced nitrate to nitrite and was inert in carbohydrate fermentation and oxidation testing. The organism was found through disc diffusion testing to be sensitive to ampicillin, gentamicin, tetracycline, chloramphenicol, erythromycin, kanamycin and carbenicillin, and was resistant to

cephalothin, methicillin, penicillin and clindamycin.

Discussion

The group of organisms now called Campylobacter were originally assigned to the genus Vibrio, but were later shown to be biochemically and culturally distinct from the type species of the genus Vibrio cholerae. Campylobacter organisms are divided into three species:[4] fetus, sputorum and fecalis. C. fetus is the only one of these species pathogenic for man. It is divided into three subspecies: Campylobacter fetus fetus, Campylobacter fetus intestinalis and Campylobacter fetus jejuni (formerly called "related vibrios"). Of these three subspecies, only intestinalis and jejuni are pathogenic in humans. C. fetus has been known to cause disease in animals since the turn of the century, but infection in man was not recognized until 1947.[5] Since then, approximately 100 cases of illness in humans resulting from C. fetus have been reported.

Gastroenteritis caused by C. fetus was probably first described in 1957 by King,[6] when she noted that seven of 19 patients with bacteremia resulting from Campylobacter had diarrhea. Additional sporadic reports[7-11] suggested that C. fetus caused enteritis, but in each instance, as in our own case, the diagnosis was established by the presence of Campylobacter organisms in cultures of blood specimens rather than stool specimens. It was not until 1972 that Butzler and his colleagues in Belgium developed a selective coproculture technique that made primary isolation of the organism from feces possible for the first time.[12] Their methods involved plating a millipore filtrate of stool on blood-thioglycolate agar that contained bacitracin, polymyxin B, novobiocin and actidione. Subsequently, the Belgians studied fecal specimens from 800 children and 100 adults with diarrhea for the presence of Campylobacter organisms and common enteric pathogens.[13] A total of 1,000 children without diarrhea served as controls. Campylobacter organisms were cultured from 5.1 percent of the children and 4 percent of the adults with diarrhea and from 1.3 percent of the controls.

Later, Skirrow[14] in England found that filtration of stool specimens could be abandoned in favor of a culture medium made highly selective for Campylobacter by the addition of vancomycin, polymyxin B and trimethoprim. Employing this technique Skirrow determined that diarrhea in 6.7 percent of 803 patients could be attributed solely to C. fetus, while in 6.2 percent of the patients other pathogens were isolated. In contrast, C. fetus did not grow from the stool specimens of 194 control subjects. In 66 percent of the C. fetus infections, fever and malaise appeared up to 24 hours before the onset of diarrhea. The feces were generally watery and offensive, but only occasionally bloody. The diarrhea usually lasted three days, but abdominal pain and malaise often lasted longer. Most patients were disabled for 10 to 14 days and person to person spread of the infection was documented. Skirrow concluded that if the fecal samples received in his laboratory were typical of those in the rest of the country, then C. fetus might be the most common identifiable cause of bacterial diarrhea in England.

Recently De Mol and Bosmans[15] delineated the importance of C. fetus as an enteropathogen in children living in a developing country. In a study of 262 children in Rwanda, Africa, Campylobacter was found in 11 percent of 204 patients with diarrhea and in none of 58 children without diarrhea. As in the clinical observations of Skirrow,[14] the African study showed that Campylobacter was the agent most often found in patients in whom gastroenteritis was protracted or in whom diarrhea was associated with severe abdominal pain.

Other studies from Africa,[16] as well as from England,[17] Canada[18,19] and Belgium,[20] have reported nearly comparable rates of enteritis resulting from Campylobacter. The most extensive of these surveys, conducted by Lauwers and coworkers[20] in Brussels, involved an examination of 22,000 stool specimens. Campylobacter organisms were isolated from 5.9 percent of diarrheal stool specimens and from 1.3 percent of normal stool specimens. As did Skirrow,[14] the Brussels workers found positive stool cultures among contacts of patients with Campylobacter enteritis; indeed, they found outbreaks of diarrhea caused by the organism in day-care nurseries. In addition, these investigators noted only seven cases of C. fetus bacteremia during their five-year investigation of infectious diarrhea. This confirms the importance of using cultures of stool specimens rather than cultures of blood specimens in diagnosing the disease.

There is limited information on the antimicrobial susceptibility of C. fetus. Using an agar dilution technique, Chow and associates[21] determined that 11 recent clinical isolates were extremely sensitive to the tetracyclines and aminoglycosides,

and generally sensitive to clindamycin, chloramphenicol, metronidazole, carbenicillin, ticarcillin and ampicillin; they were relatively resistant to penicillin and cephalosporins, and highly resistant to vancomycin. Based on these and our own *in vitro* data we decided to treat our patient with a tetracycline. However, definite recommendations for optimum treatment of Campylobacter enteritis can be made only after further clinical experience.

Conclusion

Campylobacter fetus seems to be a recently discovered important cause of infectious diarrhea in England, Belgium, Africa and Canada. However, the incidence of Campylobacter enteritis in the United States is still unknown. This can be partly explained by the fact that campylobacteriosis is not a reportable disease in this country. Yet it is also apparent that microbiology laboratories in the United States do not routinely use the newly developed selective media for isolation of the organism. We have decided to adapt the coproculture method of Skirrow, therefore, and search for Campylobacter in stool specimens from patients with or without gastroenteritis to assess the importance of the organism as a cause of diarrhea in our own locale.

Addendum

While preparing this manuscript for publication the Center for Disease Control reported preliminary findings on an outbreak of acute gastroenteritis involving as many as 2,000 residents of Bennington, Vermont.[22] Routine tests for common bacterial and parasitic pathogens were negative, but cultures made at the Center for Disease Control from rectal swabs were positive for C. fetus subspecies jejuni in five of nine cases. None of the 20 rectal swabs from the healthy residents used as controls in testing was positive. This report may represent the first recognized outbreak of Campylobacter diarrhea in the United States.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgment before publication.

Cults, Armageddon and the Holocaust

TO THE EDITOR: Dr. Michael J. Franzblau, in his letter "Of Cults and Armageddon" in the April 1979 issue, attempts to analyze the motives of the creators of the Holocaust. His conclusion is that "the Polish-German people supported these actions coolly and with malice."

Dr. Franzblau makes a great mistake and he commits a grave injustice by equating the role of the Polish people with the role of the German people in the mass murders committed during the Holocaust. The Holocaust was conceived and organized by the Nazis, who were Germans. The Poles, themselves victims of mass murders, were helpless to stop them. Thousands of Poles were murdered by the Nazis for trying to hide Jews. Their courage and self-sacrifice should be remembered and respected because detection of a Jew in a Polish home in those days meant instantaneous death to the entire Polish family.

Yes, there existed antisemitism in Poland, and there were informers and traitors among Poles, as they existed among all other nationalities. But it is unfair, unjust and ugly to condemn a whole nation for the actions of a few.

We cannot correct injustice by creating new prejudice and new hate.

OTTO E. LAUTERBACH, MD
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Treatment of Nongonococcal Epididymitis

TO THE EDITOR: The March 1979 issue contains the latest Public Health Service recommendations for the treatment of gonorrhea.[1] Suggested empiric therapy for nongonococcal epididymitis is tetracycline, 0.5 gram four times a day for ten days. I feel this is worthy of further evaluation.

Tetracycline therapy is appropriate for chlamydial epididymitis, the most frequent cause of acute epididymitis in men under 30 years of age.[2] In men over 35 years coliform organisms are the etiologic agent in the majority of cases.[2] Tetracycline may not be appropriate empiric therapy for such patients. In our hospital in 1978, for example, only 61.5 percent of strains of Escherichia coli were sensitive to tetracycline, while 72, 72.5, 89 and 99.3 percent were sensitive to ampicillin, sulfisoxazole, trimethoprim-sulfamethoxazole combination and gentamicin, respectively. Tetracycline was also the least active *in vitro* against other coliforms. Any of the last four antibiotics might be more effective empiric therapy for men over 35 years of age. The authors might also have mentioned the use of epididymal aspiration, a simply performed bedside technique, for diagnostic purposes in unclear or refractory cases.

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Youthful Smokers

TO THE EDITOR: In his comments titled "Another Cowboy Selling Cancer" in the Correspondence section of the March 1979 issue, Dr. Frankel points up the perils of just putting a pinch of snuff between the teeth and the cheek. We are reminded that snuff, rather than being a pleasurable and harmless substitute for cigarettes, can actually be carcinogenic. My first shocked reaction to this was "Why doesn't the government do something about it?"

Now turn about and take a second look at cigarette advertising. Here, too, the hairy chested, cigarette smoking cowboy rides off into the sunset, carrying the unmistakable message to every adolescent that cigarette smoking equates with male macho. And for the girls Madison Avenue serves up slim and sylph-like symbols, invariably holding long cigarettes in carefully manicured, stain-free fingers.

What subtle soft sell. As a result, more and

more boys and girls (especially girls) are acquiring a cigarette habit early in life. And lung cancer rates for women are steadily climbing. Why doesn't someone do something about this?

Some periodicals, *Sunset* magazine, for example, simply do not accept cigarette advertising. And they seem to prosper. In France the use of human figures in cigarette ads is prohibited by law. In some Canadian provinces the dispensing of cigarettes through vending machines is forbidden. The Swedish government recognizes the folly of telling youngsters that something "may be dangerous to your health." That, to juveniles, is a challenge to try it. The Swedes also know that this same cigarette warning in fine print is easily ignored. Therefore, they now have 16 differently worded warnings that must be displayed in bold print, and changed regularly. The word "cancer" is to be included. Sly tactics, but they just may succeed.

Somehow or other we must deglamorize smoking. The American Medical Association, so successful in its vigorous campaign against violence on television, seems less eager to do battle with this more deadly foe. Secretary Califano of the Department of Health, Education, and Welfare repeatedly bludgeons the public with more statistics, but the rate of cigarette consumption continues to rise; emphysema, heart disease and lung cancer are on the increase. Six million young people, many under age 12, are cigarette smokers and their numbers are increasing.

Why, oh why, doesn't somebody *do* something?

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Ulcerative Colitis and Pericarditis

To the Editor: It was with great interest that I read the recent article by Levin and co-workers "Pericarditis in Association With Ulcerative Colitis" (130:369-370, Apr 1979).

In 1975 I evaluated a 30-year-old man, in whom ulcerative colitis had been well controlled on a regimen of sulfasalazine (Azulfidine), for chest and upper back pain and found evidence of cardiomegaly with an associated pleural effusion. Although a cardiogram was normal, echocardiography showed evidence of a pericardial effusion. Skin tests subsequently were negative for coccidioidomycosis and tuberculosis. Consideration was given to tapping the very small pleural effusion; however, it had resolved by the next day. Treatment with indomethacin (Indocin) was also considered, but the patient's low-grade fever had defervesced as well in 36 hours and he was essentially asymptomatic by that time.

In retrospect, the patient had had a documented bout of pericarditis when he had been admitted to hospital at Stanford in 1973, at which time ulcerative colitis was also minimally symptomatic, and his symptoms were mainly those of chest and arm pain at that time as well. While viral studies were not done during either of these episodes, it would seem that in this patient relapsing pericarditis was more likely associated with inflammatory bowel disease—that is, ulcerative colitis. Interestingly, in this patient there has been no evidence of other extraintestinal manifestations of the inflammatory bowel disease, at least to date.

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Refer to: Bromberg W: Functional overlay: An illegitimate diagnosis? (Forensic Medicine). West J Med 130:561-565, Jun 1979

Functional Overlay: An Illegitimate Diagnosis?

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Functional overlay is not a recognized psychiatric diagnosis. Evaluating functional overlay and differentiating between this concept and organic conditions is important in medicolegal areas in which financial values are placed on pain and disability. Functional overlay is not malingering: the former is based on preconscious or unconscious mechanisms, the latter is consciously induced.

In considering psychologic reactions to pain and disability, a gradient of simulation, malingering, symptom exaggeration, overvaluation, functional overlay and hysteria is useful. The dynamics of overlay are a combination of anxiety from body-image distortion and depression from decreased efficiency of the body, as well as the resulting psychosocial disruption in a patient's life.

THE DESCRIPTION *functional overlay* is an out-of-wedlock term, a bastard offspring of malingering and hysteria. Neither the current *Diagnostic and Statistical Manual of Mental Disorders* by the American Psychiatric Association (*DSM II*, 1968)[1] nor the thoroughly revised third edition of the manual, still in draft form,[2] includes this term. Hinsie's *Psychiatric Dictionary*[3] does not define the phrase, nor does Dorland's *Medical Dictionary*.[4] Although the literature regarding this condition is sparse, functional overlay is a matter of daily experience for physicians, especially orthopedic surgeons, neurosurgeons, neuropsychiatrists and physiatrists working with medicolegal matters. Formal medicine does not acknowledge the term. Nonetheless, the need to advise courts and attorneys, who attempt to assign financial values to pain and disability, forces physicians to accept the concept.

There are no medical tests to measure the extent of emotional reactions to injury: functional overlay cannot be confirmed objectively. It is not a diagnosis. Still the concept has concrete meaning in medicolegal areas and physicians are called upon to assist the law in differentiating between legitimate diagnoses and descriptive phrases such as functional overlay. A case chosen from hundreds seen every day by those who deal with traumatology will illustrate the problem of evaluating functional overlay.

Report of a Case

A divorced woman in her 50's was driving a car at a slow speed when the left front wheel was struck by a car rounding a corner. The impact was minor. She was bounced around, striking the door jamb to her left with her head. She felt

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dazed but did not lose consciousness. For three days she did not seek medical help even though headache, numbness in the right hand and leg, double vision (reportedly), neck pain, fatigue and nervousness occurred. Examination by her practitioner resulted in a diagnosis of "transient cerebral ischemia" following "whiplash." Conservative treatment was of no benefit.

The woman was referred to a neurosurgeon, an orthopedic surgeon, a neurologist and a physiatrist. A full workup (scan, x-ray studies and the like) in a hospital showed no abnormalities. Cervical x-ray films were normal and "moderate degenerative osteoarthritis" of the lumbar spine was noted. The neurosurgeon found the results of examination "essentially negative"; the orthopedic surgeon diagnosed "radiculopathy" in the cervical area; the physiatrist found possible carpal tunnel syndrome, with indications of hysteria; a neurologist diagnosed "possible radiculopathy with functional overlay"; the primary care physician diagnosed "posttraumatic headache."

Symptoms continued unabated for two years. The patient said that she had difficulty concentrating, and that weakness in the right hand (to the point of being unable to hold a pencil), nervous tension and persistence of the original symptoms were present. Finally, as a result of disability, she had to retire after 20 years as a statistician. During the two years following the accident her work, which until then had been reported as outstanding, had deteriorated. Retirement resulted in embarrassment, depression and especially a loss of the companionship of her fellow workers ("They were my daytime family," she explained).

Her medical history indicated treatment of hypertension, tachycardia, cerebral arteriosclerosis, arthritis, nervous tension and kidney problems, none of which had interfered with her work or social life until the accident, 1½ years before retirement.

Though the patient had not been negligent and had not caused the accident, on examination two years later she was depressed and tense, and had bitter complaints regarding her condition. She had always been proud of her self-sufficiency, health, professional proficiency, and capacity for friendship with supervisor and co-workers—and these all were destroyed. The weakness of her right hand was her greatest physical concern.

Results of neurological examination showed a few signs of questionable significance: the right hand was extremely weak with no change in reflexes, sensory deficit, limitation of movement, organic tremor or actual motor impairment. The deterioration that the patient said she felt could not be shown on repeated examination. A *diagnosis* of functional overlay was confirmed.

It was clear that the patient's disabilities had psychologic roots; for example, unanticipated low self-esteem, confirmed when separation anxiety developed after the patient's retirement. The clinical problem was to estimate whether the persistence of symptoms related to the accident.

Discussion

In distinguishing between malingering, functional overlay and hysteria, medicolegal experts may join some attorneys and other nonmedical persons in regarding functional overlay as a meretricious claim on the part of a disabled litigant. Others may seek explanations in the murky waters of the unconscious. In any event, the concept of functional overlay is shadowy, less malingered than malingering, less neurotic than hysteria, and yet seemingly partaking of both. In short, functional overlay is a pariah in the universe of respectable diagnoses.

Barham Carter, writing in 1967 in the *Lancet*,[5] identifies functional overlay as lying "between general medicine, neurology and psychiatry . . . a borderland difficult to define . . . belonging to none of these disciplines." He offers the following classification of such conditions: (1) conversion reactions of hysterical type, (2) anxiety and depressive reactions and (3) environmental-stress reactions—that is, personal and financial problems. Carter urged that "more time than usual be spent in evaluating functional overlay . . . [and] a change in the attitude of vague annoyance and resentment . . . common among some doctors towards these patients."

Another British investigator, Henry Miller,[6] reviewed 4,000 cases of *accident neurosis* (1961) in which malingering and "gross functional complaints following injury" were evaluated. This phrase can be construed in American usage as functional overlay. Miller and Cartlidge[7] stated in a 1972 paper that "simulation, exaggeration and willfully false . . . symptoms" were closely allied. No mention of functional overlay as such was made in the paper but the authors' views are shown in their statement that "medical simulation occurs only where it is hoped that it will yield personal or economic gain." Presumably,

Miller and Cartlidge included primary and secondary gain as motives for simulation.

It is fair to say that most physicians would agree that gain of some kind is a factor in all the conditions under discussion. In the older literature on the subject, simulation, malingering and hysteria were lumped together as manifestations of gain. Therefore, Walter Schaller, in the *Journal of the American Medical Association* stated in 1939[8]

> Every posttraumatic neurosis is not malingery, but a subconscious simulator . . . every hysteric is a simulator [representing] a milder implication of motive and conduct [than found in] the malingerer.

The more moderate view, voiced in Noyes[1] classic psychiatric text (1955),[9] is

> Some hysterical phenomena are on the borderline between psychoneurotic reactions and simulation and therefore come close to malingering. Just where as to awareness, the line between simulation and hysteria should be drawn is therefore often arbitrary.

As Noyes hinted, malingering itself can be considered a kind of neurosis.

To begin with, various states can be plainly defined. *Simulation* is a state in which a person assumes pain and disability; it is an imitation of illness without a cause or organic basis. *Malingering* is also a state in which a person feigns illness but the assumed state may be based on a preceding event—for example, an injury. For practical purposes the terms *simulation* and *malingering* are synonymous. *Exaggeration* is a magnification of pain and disability. *Overvaluation* represents a reaction to pain which may seem feigned but is not. *Functional overlay* is an emotional superimposition on the original symptoms of an injury or illness. *Hysteria*—that is, conversion hysteria—is a physical representation of an emotional conflict.

One further condition requires consideration in these distinctions, namely *psychophysiological disorders,* defined in the American Psychiatric Association's *DSM II* as "caused by emotional factors . . . usually under autonomic nervous system innervation. . . ."[1(p48)] Examples are paroxysmal tachycardia, hyperventilation, irritable colon and the like. Here the autonomic nervous system produces symptoms commonly associated with anxiety in which the condition is neurogenic and not primarily psychogenic.

A Gradient of Psychiatric Reactions

Obviously, an infinite variety of overlapping occurs in these conditions. The task of differentiating each reaction is made more difficult by the fact that a gradient exists in reactions to pain and disability, starting with simulation, followed closely by malingering, exaggeration and overvaluation and, finally, functional overlay and hysterical neurosis. The gradient parallels changes in motivation from conscious maneuvering to the influence of preconscious and unconscious mechanisms. The first three steps in the gradient are characterized by goals of primary gain and the last three by goals of secondary gain. The legal problem is determining the validity of each reaction in relation to court settlements and awards. The psychiatric problems, more narrowly, become the degree of stress on the ego caused by the injury or illness.

The medical experts' task is to measure deviations from *normal* as it is understood by the examiners. In essence, the task involves interpreting how much emotional reaction is normal. Generally, such interpretations are based on medical knowledge derived from vast experience with illnesses and injuries and tinctured by varying degrees of intuition. In such cases, intuition is sometimes aided by a physican's personal experience with injury as well as a complex syncytium of social attitudes, cultural influences and biases. In any event, the judgment is generally regarded as correct and is used to establish the amount of pain and disability a patient may suffer from a particular injury. It is fair to say that this estimation of the intensity and duration that a patient *should have* suffered has been relied on by the courts.

There is a problem with the concepts of *average* and *normal* in relation to the highly subjective character of pain. *Webster's Third New International Dictionary* defines normal as "conformed to a type, standard, or regular pattern" and the *Oxford English Dictionary* defines it as "according to a norm." Koranyi,[10] in a recent article, "The Normal and Its Deviations," tried to find acceptable criteria for normality in measuring mental reactions. He quoted, among others, Marie Jahoda's attempt to define normality as "Absence of mental illness, normalcy of behavior, adjustment to environment, internal unity of personality and correct conception of reality." From this tautologous statement and other more cryptic definitions, Koranyi concluded that the concept of normality is a "known ambiguity." However, lawyers, physicians and others recognize certain dimensions of normality. To this am-

biguity we may add that reactions to pain and disability are highly individual and each patient regards his reaction as normal.

Effects on Body Image

This attitude is not necessarily meretricious or self-seeking. It receives force from a preoccupation with the effects of injury on the body image. Paul Schilder,[11] working with Henry Head's concept of postural model (body schema) that is built up of sensory impressions including proprioceptive sensations, studied body-image distortions in patients with organic and psychological disease. He showed how intoxication, injury, brain disease, as well as neurosis and psychosis, altered the body image, the "tri-dimensional image everybody has about himself." The optic, tactile, proprioceptive and vestibular sensations, which make up the body image, form a gestalt which lies quiescent in the psyche until a disruptive event distorts the image and brings it to consciousness. Such distortions give rise to varying degrees of anxiety. Common examples are seen in intoxication by alcohol (hallucinosis),[12] and in toxic states from methaqualone, phencyclidine (PCP) and the like. Sensations are at first exhilarating, then become alarming as enlargement of the head, lengthening or shortening of the limbs, space and time expansion or contraction, and anesthesia or paresthesia distort the body image. Rupture of body-image integrity jars a person's narcissism (primary narcissism in Freud's terminology) and results in anxiety and panic.

Pain added to the dysesthesia outlined above enhances anxiety from body-image distortion. Pain within or on the surface of the body frequently brings about an overemphasis of the injured area. To the patient an aching gut is all absorbing; edema appears enormous; hemorrhage is frightening; a fracture is irreparable. A sufferer's immediate reaction is to physically protect the area injured. A parallel psychological reaction (Schilder) is neglecting sensations from the rest of the body in favor of those from the injured area—that is, the libido flows to the painful organ. Gestalt psychologists explain this automatic mechanism as a move of the injured part into the foreground of perception. In modern psychiatric parlance (1978)[13] the "fixed mechanical-organic belief structure with regard to bodily functions and malfunctions" is stimulated. Therefore pain, when persistent, brings the body-schema distortion closer to the perceptive ego. The series of psychological events sketched above forms the basis for functional overlay.

Sociopsychological Aspects

In addition, certain sociopsychological attitudes support the development of functional overlay. A patient who suffers disability and pain has an alteration in his social attitudes, the so-called "personality change." Workers in pain clinics have observed the same realignment of life patterns in patients with the chronic intractable benign pain syndrome (CIBPS). Here, in the absence of demonstrable disease or physiological abnormality, "pain is both a function of and a stimulus to abnormal illness behavior" (Sternbach). Pinsky[14] expresses the predicament as "The CIBPS patient seems to have ongoing pain and suffering as its corner stone, accompanied by progressive psychosocial upheaval. . . ." When a patient with chronic intractable benign pain syndrome is involved in litigation, certain specific sociopsychologic trends can be identified. The most notable is resentment, particularly in cases in which the accident was unanticipated and caused pain.

A patient projects his hostility, whether suppressed or expressed, on the "enemy," an equipment failure, uncontrolled drivers, assailants or fate. These attitudes expand to include the third parties (insurance companies), attorneys on both sides, the legal system, examining physicians and the courts. Attitudes related to paranoia that are not truly delusional spread to society. Long repressed hostilities based on previous accidents surface and a patient's personality takes on a fixed stance of irritability and vague antisociality. The trauma patients are depressed, impatient, and alternately belligerent toward and dependent on the physician. They address themselves unconsciously to the community through irritability toward the family, medical personnel and attorneys. In the medical office, a patient's irritation is shown by lack of cooperation during an interview or examination, questioning the competence of the examiner or open opposition. On the other hand a patient may be cloying, passive or ingratiating: he becomes resigned to numerous examinations, depositions and conferences required in complex medicolegal problems.

If hostility is aroused in a patient by time-consuming negotiations, attorneys may suspect

that the patient is feigning illness or has excess interest in financial awards. If a patient is re-signed, attorneys may suspect that the patient's condition is hysterical. Experience with hundreds of trauma patients has shown that the intricate reactions and counterreactions indigenous to the local process do influence functional overflow. From a patient's position, it is undeniable that a sufferer of an accident is equipped with less strength of ego to face his problem after the injury.

What emerges is the concept that functional overlay represents a complex sociopsychological reaction compounded of unconscious dependence, anxiety from body-image distortion, resentment and a revival of faintly paranoid attitudes toward society in persons involved in accidents. It should not be confused with malingering or conversion hysteria.

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Refer to: Conant MA, Fine DJ: The hoptel really works: A commentary (In the Forefront). West J Med 130:566-569, Jun 1979

The Hoptel Really Works: A Commentary

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THE UNIVERSITY OF CALIFORNIA, San Francisco (UCSF), Hospitals and Clinics have developed a program of boarding Medicaid (known in California as Medi-Cal) patients in private guest houses near the university campus. The program has worked well since November 1975 and is estimated to have saved more than $100,000 in public funds. The purpose of this paper is to recount the history of the hoptel program, to explain how funds for this program were originally obtained and to suggest guidelines that other hospitals might wish to use in implementing a similar program.

The Problem

UCSF is a major referral center for Northern California with 20,000 admissions per year. A large percentage of the patient load is made up of patients with unusual and difficult diagnostic and therapeutic problems. Many of these patients have expended all of their personal resources for health care and are now insured by Medi-Cal or similar government programs. Frequently the nature and extent of the patient's illness has resulted in significant social problems which must be appreciated by the attending physician and dealt with by ancillary professional personnel.

As the Utilization Review Committee at UCSF became more active, it found a large number of patients who were referred from great distances and were admitted to the hospital by their attending physicians. A review showed that evaluations could be done in these cases in the outpatient clinic over a period of three to five days, but that the patients could not afford a hotel room in the San Francisco metropolitan area and they could not be expected to commute from an area as remote as the Mendocino coast every day. Physicians at the hospital, when confronted with this problem, were taking the only action that was left open to them and admitting the patients to the hospital for a three- to five-day workup. This, of course, was resulting in a cost to the state of approximately $185 per day for board and lodging.

The Solution

The solution to this problem was already contained in existing Medi-Cal legislation. As early as July of 1975 the state Department of Health had issued directives[1] that allowed hospitals to board Medi-Cal patients at the long-term rate of $22 a day. In this directive a "hoptel" (hospital and hotel contraction) was defined as a unit or section of an acute care hospital used for patients who do not require the acute level of care, but do require some degree of acute hospital services only available on an inpatient basis. The state published four criteria to be used when this new service was employed:

1. "The medical condition of the patient requires selected acute hospital services for the diagnosis and/or treatment of disease, but does not require all services provided at the acute level."

2. "The patient's living circumstances, travel

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or medical transportation problems make institutional care less costly, particularly at long-term care rates."

3. "The hospital rate charged does not exceed long-term rates."

4. "The patient's treatment needs require close proximity to the hospital, e.g., daily radiation therapy, close observation, including hospital laboratory services."[1]

The new hoptel designation with payment of $22 a day for an acute care hospital bed was fine for the state, the patient and the attending physician, but in an era when hospitals charge $185 a day, it is obvious fiscal suicide for a hospital administrator to agree to fill those beds with patients who pay only $22.

It became obvious that permission was needed from the state to use the $22 a day hoptel rate to place the patient in a hotel, boarding house or guest house near UCSF and to use those funds left over to help pay for the patient's meals, any transportation costs that might be incurred in getting the patient to and from the guest house, and any administrative costs incurred by the hospital in supervising the program and billing the state for the services.

UCSF wrote to Mr. Mario Obledo, the Secretary of the California Department of Health and Welfare in August 1975, requesting permission to use hoptel funds for the establishment of off campus room and board services for Medi-Cal recipients. Favorable response was received from Mr. Obledo's office on September 5, 1975, and the question was referred to Dr. Jerome Lackner, Director of the Department of Health, for implementation. Dr. Lackner gave permission to devise a proposal and submit it to the state for approval. A program was approved late in 1975 and has now been in operation for more than two years. The California Department of Health recently made this a statewide benefit when they stated "the Department of Health has now advised that hospitals may use any available hospital bed for (hoptel) services, set aside a specific unit or section as a hoptel, or arrange board and care for hoptel services in close proximity to the hospital."[2]

The Plan

A plan was developed which delineated each of the constituents of the proposal in a concise manner and was submitted to the state Department of Health for approval. All of the guest houses within a four block radius of UCSF were identified and asked to participate in the program. To date, the four guest houses that have joined in the program have been sufficient to handle all of the patients that have been included in the hoptel program. If the boarding requirements ever exceed the local capability, UCSF will explore with Medi-Cal the use of some of the hoptel fee for public transportation or the feasibility of Medi-Cal financed van service to and from a hoptel.

Any patient who lives more than 50 miles from UCSF who needs care that could be provided as an outpatient, or patients who need numerous laboratory tests that would take a number of days to complete, are considered for inclusion in the program. Approval for some patients living closer than 50 miles who for one reason or another are not able to get back and forth for their treatments or evaluation has also been obtained.

When a physician has a patient he wishes to enroll in the hoptel program, he submits a completed form (MC170) to the Medi-Cal consultant through the Utilization Review Office. When the Medi-Cal consultant has approved the necessary days for the treatment or evaluation, the completed form goes to the Social Service Office. The social workers make reservations in the guest house and, in turn, inform the physician's office of these arrangements. The physician can then schedule the necessary studies to get the most expedient utilization of the time he will have the patient available.

The Social Service Office issues meal tickets to each of the hoptel recipients and these can be presented to the UCSF cafeteria for breakfast, lunch and dinner. We have assigned a face value of these tickets of $1.50 for breakfast, $2.50 for lunch, and $3.00 for dinner. A "hold harmless" agreement explaining that UCSF is not responsible for the operation of the guest house is given to the patient for his signature. This document was drawn up by legal counsel and a copy is shown as Figure 1. After the last approved day of each stay, the guest house proprietor is instructed to send a bill for each hoptel patient to the hospital's Accounts Receivable Department. Reimbursement to the guest house is paid within ten working days. In turn, the state is billed for a regular hospital stay at the hoptel rate level. A patient comment card is mailed to each patient who has participated

in the program. Virtually all have replied with very favorable remarks.

Utilization

The hoptel service has been used most frequently for patients receiving long-term treatments rather than for patients who need extensive outpatient medical workups or presurgical evaluations. The services most frequently using the hoptel program have been radiation therapy, oncology and dermatology. Many patients who have started radiation treatments in the hospital have improved to the point that they can be discharged from the acute care center and complete their radiation therapy as outpatients. This, of course, allows a patient to continue being treated by the same team of radiotherapists and on the same machine that has already been calibrated for his therapy. Cancer chemotherapy patients can be admitted to the hoptel between treatments with systemic antimetabolites. Dermatological patients being treated with the Goeckermann program can be admitted to the hoptel unit for completion of their therapy in UCSF's dermatology day care center.

A few physicians have utilized the hoptel service for boarding patients during extensive outpatient diagnostic evaluations. The utilization of the hoptel program for this service has not grown and it is our impression that most of UCSF's medical consultants are seeing Medi-Cal patients and then returning the patient to his local physician with suggestions for diagnostic studies to be carried out in the patient's community.

The surgical services have not utilized the hoptel program to any major degree. Most surgical patients admitted have had their preoperative medical evaluations done by their local physicians and they are admitted the evening before operation. Attempts have been made to encourage the surgical services to bring high-risk surgical patients for an outpatient evaluation a day or two before operation and keep these patients in the local hoptel facilities. To date, this has not become popular.

The availability of hoptel services has proved of great comfort to those on the utilization committee of the hospital and to the state-appointed Medi-Cal consultants. In the past these physicians

HOPTEL PROGRAM

Patient Consent Form

I am presently eligible, to the best of my knowledge, for Medi-Cal benefits and I have requested diagnostic testing or treatment on an outpatient basis at the University of California Medical Center. Upon my request, a room reservation has been made in my name at _____

_____

which has agreed to accept reimbursement from Medi-Cal funds for approved room charges which I incur as a result of my staying in the area in order to receive diagnostic testing or treatment at the University of California Medical Center.

I understand and agree that the University of California is not connected in any other manner with such guest homes, and assumes no responsibility or duty for the condition of the guest homes, transportation between the hospital and guest home, or for any incident arising out of or in connection with my stay at one of the guest homes. I further understand and agree that the University of California is not responsible for any charges I may incur at the guest home in the event Medi-Cal benefits for such room charges are not paid by Medi-Cal.

Signed _____

Dated _____

Figure 1.—The agreement signed by patients for the hoptel program.

sympathized with attending physicians who felt that they had no option but to admit an indigent patient to the acute facility for workup. Now, if that course of action appears to be inappropriate, physicians can be offered a viable alternative so that the evaluation and care of patients can proceed uninterrupted.

Conclusions

Experience with outpatient boarding of patients who need diagnostic and therapeutic procedures done over a period of days has been extremely favorable and more than 800 patient days of hoptel care have been offered since the program's inception. We feel that this has worked well for Medi-Cal patients who must travel great distances for care. It has worked well for physicians who are given some option for boarding their patients during treatment and evaluation and, of course, it has saved the state's taxpayers the difference between $185 a day for an acute care bed at the hospital and the $22 a day that is expended for the hoptel. This is a net savings since medical overhead costs for review of inpatient or hoptel days are the same. This same type of arrangement could be investigated by any major referral center and any community hospital serving an area where patients are forced to travel long distances for evaluation and care.

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Maggots for Debridement

WE HAD ONE case that we reported in the *Archives of Otolaryngology* a couple of years ago. The patient had come into the hospital with an acute infection of his ear canal from trauma from a hearing aid. This progressed to malignant external otitis. He had had a simple mastoidectomy and a course of carbenicillin and gentamicin, and the condition had shown improvement. He came back in after he had been out of the hospital for six weeks and a relapse had occurred. We reoperated, before we knew better than to do that, and were left with a wound that would not heal. Carl Horn got tired of debriding this cavity every day as a rotating student on our service, and listened to some stories we were telling about the use of maggots as very active debridement agents. Carl's an enterprising guy, so he said it would be simpler for him to grow the maggots and put them to work. We got all the material out and got the eggs from houseflies, which we procured from Texas A&M to make sure they were not screw worms and were the proper type of fly. We took the eggs and sterilized them in formalin and grew them on sterile meat dishes until the larvae hatched. Then we put these in this guy's ear. They itched something fierce, but we kept them on there for about four days, until he couldn't stand it any longer, and then we took all the maggots out. The cavity in this short period of time totally filled with good healthy granulation tissue. We put a skin graft on it, and five days later the patient was out of the hospital. It is now four years since we've treated him, and he has done quite well.

—GEORGE A. GATES, MD, *San Antonio, Texas*

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Medical Information

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An A,B,C,D of Cancer Chemotherapy

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ONE OF THE major highlights in the management of metastatic cancer during the last few years has been the development of four new chemotherapy drugs. Their addition to the therapeutic armamentarium of chemotherapists who treat patients with cancer has led to palliation and rates of complete and partial tumor regression never before possible. However, such agents should be used only by physicians familiar with the drugs and their toxicities. The following will emphasize important features of these four agents, referred to as the *A,B,C,D* of new cancer chemotherapy (Table 1).

The *A* of this group refers to doxorubicin hydrochloride (Adriamycin),[1] an antibiotic of the anthracycline group isolated from a culture of Streptomyces organisms and developed in Italy. Currently marketed in the United States by Adria Laboratories Inc., it is an analogue of daunomycin, a drug supplied by the National Cancer Institute, which is helpful in the management of acute leukemia in adults.

Adriamycin appears to exert its antitumor activity by binding to DNA through intercalation between base pairs, and by inhibiting RNA synthesis by means of steric hindrance and template disordering. There is extensive tissue binding by this drug, and it is metabolized predominantly by the liver. Prolonged plasma levels, therefore, are associated with exaggerated clinical toxicity. The usual dosage is 40 to 60 mg per sq meter of body surface area* given intravenously every three to four weeks.

Adriamycin is a red powder packaged in 10 mg and 50 mg vials. It is an expensive drug, with the current average cost of $16 and $74 for 10 mg and 50 mg vials, respectively. The drug should be reconstituted with sterile water or saline solution. Such solution is stable for 24 hours at room temperature and for at least 48 hours when kept in the refrigerator. Adriamycin as a powder is stable at room temperature.

The drug should be administered into a freely running intravenous infusion line in which the flow is 5 percent dextrose or normal saline solution, or both. Correct infusion technique is mandatory because extravasation of this drug is not only painful, but leads to massive tissue necrosis and slough. Adriamycin is incompatible with heparin and methotrexate, forming a precipitate with either of these medications.

The spectrum of activity against metastatic cancer is notable with this drug. Adriamycin, when combined with cyclophosphamide or other drugs effective in treatment of cancer of the breast, has produced complete and partial remission rates that are among the highest ever achieved.[2] It is also an agent of choice for patients with metastatic carcinoma of the thyroid and the bladder.[1]

Adriamycin has been incorporated into virtually every treatment program for the management of sarcoma. Indeed, its response rate has been so impressive that it is incorporated into adjuvant programs for the prevention of recurrent osteogenic sarcoma. It is noteworthy that the best response rates in sarcoma patients have been obtained when adriamycin has been combined in a program with dacarbazine,[3] one of the new drugs to be discussed later.

Adriamycin has shown significant activity in the management of Hodgkin disease refractory to conventional therapy with a combination of mechlorethamine, vincristine (Oncovin), procarbazine and prednisone (MOPP).[4] Studies now suggest that when combined with bleomycin, vinblastine and dacarbazine, it produces initial response rates as first-line therapy fully equal to that of MOPP. Adriamycin is also active in the management of malignant lymphomas in both the nodular and diffuse categories.[5]

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*Body surface area expressed in square meters can be easily calculated from standard nomograms using a patient's weight and height.

The drug has also been used successfully in combination therapy for bronchogenic carcinoma in virtually every cell type.[16] Recent studies have clearly indicated that it is notably active in the management of ovarian[6] and prostatic carcinoma.[7] Again, recent evidence suggests that it is at least equal to, if not superior to, daunomycin as the initial therapy for acute myelogenous leukemia.[8]

The toxicity of this drug is striking. It produces significant nausea and vomiting in more than 70 percent of patients, and alopecia will develop in almost all cases. The loss of hair is usually not permanent and regrowth may occur even while the patient is still receiving it. In some cases both texture and color of the hair may be altered with regrowth.

Stomatitis can be a dangerous complication and must be anticipated. As with almost all chemotherapeutic drugs, myelosuppression can be severe and affects both leukocytes and platelets. As mentioned above, one must be extremely careful to avoid local extravasation of the drug because necrosis of tissue may develop. The patient should also be warned that urine may turn red within a day after drug administration. This has no pathological significance.

Cardiomyopathy is a unique feature of the toxicity of Adriamycin.[9] Results of studies have indicated that this drug causes necrosis and changes in the myocardium beginning with a total dose as low as 240 mg per sq meter of body surface area. Results of follow-up studies of patients in whom Adriamycin therapy was discontinued indicate that such damage may continue for as long as a year after administration of the drug has been stopped. The predominant clinical manifestation has been congestive heart failure which may appear suddenly and, in many cases, has been refractory to conventional therapy. In some cases death has ensued. Electrocardio-

TABLE 1.—*Features of the A,B,C,D Chemotherapy*

Adriamycin	*Bleomycin*	*Nitrosoureas*	*DTIC*
MAJOR INDICATIONS IN VARIOUS TYPES OF CANCER PERCENT RESPONSES AS SINGLE AGENT* OR (IN COMBINATION)			
Breast 35-40* (60-70)	Head and neck . 30*	Brain 45*	Metastatic melanoma 25*
Thyroid 35*	Cervix 10*	Bronchogenic ... (30-60)	Hodgkin disease .. (90)
Bladder 35*	Hodgkin disease . (90)	Metastatic melanoma .... (20)	Soft tissue sarcoma (40)
Bronchogenic	Malignant	Hodgkin disease . (90)	
oat cell 30* (60-70)	lymphoma ... (40-60)		
non-oat cell 20* (30-40)			
Soft tissue sarcoma . (40)	Testicular .....(75-100)		
Osteogenic sarcoma . (20)			
Acute myelogenous leukemia ..... (40-60)			
Hodgkin disease ... (90)			
Malignant lymphoma (40-60)			
Ovary ..... (30-40)			
Prostate 25*			
HOW SUPPLIED AND APPROXIMATE COST			
10 mg vial $16	15 mg vial $40	Box containing 2 each of CCNU of 10, 40 and 100 mg capsule $14	100 mg vial $25
50 mg vial $74		BCNU 100 mg $15	200 mg vial $43
UNUSUAL TOXICITIES			
Cardiotoxicity; 100 percent alopecia	Pulmonary and dermatologic	Delayed myelosuppression	Severe nausea and vomiting

DTIC = Dimethyl triazeno imidazole carboxamide
CCNU = 1-(2-choloroethyl)-3-cyclohexyl-1-nitrosourea
BCNU = 1,3-bis(2-chloroethyl)-1-nitrosourea

graphic rhythm abnormalities are common, most of which are nonspecific and correlate poorly with endomyocardial biopsy findings.[10]

Recently systolic time interval, the ratio of preejection period to left ventricular ejection time has been hailed by some as the most sensitive noninvasive test for predicting toxicity.[10]

Data from many sources indicate that the frequency of this problem rises notably when the total dose of Adriamycin equals or exceeds 550 mg per sq meter. Therefore, the current recommendation is that, except under exceptional circumstances, patients should not receive more than this amount of the drug. Furthermore, if radiation therapy has been given before in the mediastinum in patients older than 70, the dosage at which cardiomyopathy develops is much lower, and current recommendations call for discontinuing the drug at a cumulative dose of 450 mg per sq meter. It is interesting that children appear to tolerate higher dosages of the drug.

It has now been verified that Adriamycin is capable of producing a recall phenomenon, for example, severe skin reactions in areas previously treated with radiation. This can necessitate discontinuing the medication. Because Adriamycin is detoxified by the liver, toxicity is enhanced if full doses are administered when there is evidence of dysfunction of the liver. Therefore, half of the usual dose is recommended when the serum bilirubin level is greater than 1.5 mg per dl.

The *B* of the new chemotherapy drugs is bleomycin,[10] with the trade name Blenoxane, from Bristol Laboratories. This drug was developed in Japan and represents a mixture of antibiotics isolated from a strain of Streptomyces organisms. It binds DNA and causes inhibition of thymidine incorporation into DNA. It is unique among antitumor agents in that leukopenia and thrombocytopenia are rarely seen even with high doses.

Bleomycin is prepared as a sterile powder that can be reconstituted with 5 percent dextrose and normal saline solution or sterile water. Each ampule contains 15 units (mg) of bleomycin and is usually reconstituted with 2 to 5 ml of solution. The powder form is stable for at least two years at room temperature. There is no loss of biological activity when reconstituted solutions are refrigerated for four weeks in sterile rubber-stopped containers. Current cost of the drug is approximately $40 per 15 unit ampule.

Bleomycin can be given intravenously or intramuscularly. The latter method is associated with some brief burning pain, and a small volume must be used in order to prevent the development of sterile abscess. The usual dosage is 5 to 15 units per sq meter of body surface area administered once or twice a week.

The most common toxicity of the drug is related to the skin and mucous membrane surfaces. Mouth ulcers, rashes or hyperpigmentation of the skin may develop. Hyperkeratosis may develop at the tips of fingers and may be associated with significant pain and ulceration. In some patients this has led to gangrene. Alopecia may develop with prolonged use of the medication. Most of the skin problems gradually disappear after treatment is stopped.

Acute toxicity, usually developing within three to five hours after the injection, may be a problem and is associated with fever, chills, nausea and vomiting. If acute toxicity develops at all, it usually appears after the first dose. Treatment includes aspirin or antihistamines. Severe anaphylaxis has occasionally occurred and causes hypotension, mental confusion, fever, chills and wheezing. This is seen predominantly in patients with lymphoma; such patients should receive a test dose of one to two units of the drug when they are first treated.

Bleomycin also has a unique toxicity that limits the total dose that should be administered lest pulmonary interstitial fibrosis with severe and irreversible respiratory incapacity be produced.[11] Pathologic studies in such cases have shown prominent squamous metaplasia of the lining cells of the alveoli with prominent interstitial edema as well. This has been noted especially in patients with lymphoma, in whom x-ray films show diffuse interstitial infiltrates that may develop rapidly while the patient continues receiving therapy. Consequently, therapy with bleomycin should be followed carefully with pulmonary function tests if necessary, and physicians should not administer a total dose in excess of 250 mg per sq meter of body surface area. In patients older than 70 there is a greater chance of the problem developing and the drug must be used with extreme care.

Bleomycin has shown significant palliative activity in patients with squamous cell carcinoma, especially of the head and neck,[10] and of the cervix.[6] Unfortunately, the responses have been short-lived, rarely exceeding three months. Current research indicates that bleomycin works quite well when combined with other drugs in the treatment of cancer of the head and neck.[12] It has also

been shown to be effective, as noted earlier, when combined with other drugs in the therapy of Hodgkin disease and malignant lymphoma.[4] It has become an important component in combination drug therapy for testicular malignancies of all varieties.[13,14] Bleomycin has lent itself to a variety of drug combination programs because of its unique minimal toxicity in bone marrow.

The next new class of drugs is represented by the nitrosourea group, developed in the United States at the National Cancer Institute. The first member of this family that became commercially available, the *C* of the title, is CCNU (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea). This is now available as CeeNU, or lomustine, from Bristol Laboratories. Boxes containing two each of the 10, 40 and 100 mg capsules are currently priced at $14 each. The other drugs in the family are BCNU (1,3-bis(2-choroethyl)-1-nitrosourea) commercially available as BiCNU or carmustine in packages containing a vial of 100 mg of powder and a vial of 3 ml of diluent for $15 (also from Bristol Laboratories), and methyl-CCNU, supplied in capsules solely by the National Cancer Institute.

All three drugs are believed to alkylate with DNA and RNA. They have also been shown to inhibit certain enzymes through carbamylation of amino acids in proteins. All are administered in intermittent single dose schedules, although several are incorporated at present into multidrug regimens. CCNU and methyl-CCNU are given orally, whereas BCNU can be reconstituted with the supplied diluent (absolute ethanol) plus additional 27 ml of sterile water for intravenous injection. Unopened vials of BCNU must be refrigerated at about 4°C, and after reconstitution the drug will slowly decompose if kept at room temperature.

A unique aspect of these drugs is high lipid solubility and the relative lack of ionization at a physiological pH. This apparently allows the drugs to cross the blood-brain barrier effectively. There are no unusual antagonistic effects when combined with other anticancer agents.

Effects of toxicity include nausea and vomiting, predictable two to six hours after administration of any of the three drugs and usually lasting less than 24 hours. The toxicity is not dose limiting and is centrally mediated. Therefore, administration of antiemetic agents is usually begun at the time of, or just before, administration of the drug and is continued for 24 hours. The oral medications should be taken on an empty stomach at bedtime. It has been found that phenothiazine derivatives and other strong sedatives given before such medication will often help patients rest through the night without nausea and vomiting.

Thrombocytopenia occurs (to a level of 80,000 to 100,000 per cu mm) about four weeks after a dose and lasts one to two weeks. Leukopenia occurs about six weeks after a dose and lasts an additional week or two. Therefore, the unique feature of these drugs is that the effect in bone marrow is delayed, dose related, dose limiting and cumulative. Therefore, the drugs should be given at intervals of six to eight weeks. Previous radiotherapy or chemotherapy, or both, or infiltration of cancer cells in bone marrow, increases toxicity in the marrow and lower doses of the drugs should be administered.

Reports from the Brain Tumor Study Group have indicated that the use of BCNU, when combined with radiation therapy, has improved response rates in primary neoplasms of the brain.[16] The response rate in metastatic carcinoma has not been so notable. Apparently, the ability to cross the blood-brain barrier renders the drug first-line therapy for brain tumors. All three members of this new class of drugs have been shown to be effective in the treatment of advanced Hodgkin disease, including cases refractory to more conventional modes of therapy.[4]

Numerous reports appearing in the literature indicate that CCNU has become a valuable addition to effective therapy for carcinoma of the lung, especially oat cell carcinoma and adenocarcinoma.[17] The nitrosourea drugs have been effective in the treatment of malignant melanoma,[18] although they are not as effective as dacarbazine, the last drug to be discussed. Earlier studies have indicated that methyl-CCNU, when combined with 5-fluorouracil, produced the highest palliative responses yet obtained in the management of metastatic malignancy of the gastrointestinal tract. However, since then this view has been challenged and now it is clear that increased survival has not been achieved.[19] Studies have also indicated notable activity of these drugs in the treatment of multiple myeloma.[20]

With all three agents, blood counts should be checked before each dose and during the third to sixth week after initiation of therapy. Then decisions regarding subsequent dosage can be made and the doses can be reduced if necessary, or the interval between treatments can be increased. Other infrequent side effects include stomatitis, alopecia, mild anemia, anorexia and

increased liver function abnormalities. These drugs have also been described as producing disorientation, lethargy and dysarthria. Reconstituted BCNU solution should be administered through intravenous drip longer than one to two hours because there is burning, redness and occasional phlebitis at the injection site if the solution is given over shorter periods of time.

The fourth drug is DTIC (dimethyl triazeno imidazole carboxamide).[21] It was also developed at the National Cancer Institute and is marketed in powder form as dacarbazine, or DTIC-Dome, by Dome Laboratories. The action has not been clearly defined; possibilities include inhibition of DNA synthesis, interaction with the sulfhydryl group or acting as an alkylating agent. Results of studies show that dacarbazine is now the drug of choice for treating metastatic melanoma, where a clinical response of greater than 20 percent, has been achieved, and obtained remissions may last a long time.[21] As mentioned earlier, when incorporated with the drugs recently introduced for the treatment of Hodgkin Disease, DTIC produces response rates comparable to the standard MOPP regimen.[4] It is also an important component in combination therapy for sarcoma.[3]

Dacarbazine is packaged in 100 and 200 mg vials at a current cost of $25 and $43 per 12 bottles, respectively. The drug is reconstituted with sterile water and both must be kept refrigerated because the solution is stable for no more than eight hours at room temperature. The usual dosage has been 250 mg per sq meter of body surface area administered intravenously in less than a half hour on five consecutive days every three to four weeks. Some recent treatment protocols also call for administering the drug in a single dose of 600 to 900 mg per sq meter of body surface area every three to four weeks,[22] although documentation of comparable efficaciousness is lacking.

Invariably, there is severe burning pain along the infused vein. Nausea and vomiting are extremely severe. If the drug is given in a five-day course, nausea and vomiting are especially prominent on the first day or two, and then decrease on the subsequent days of administration. It is advisable to give the patient an ample supply of antiemetic agents during and immediately after administration of the drug. Occasionally, an influenza-like syndrome may appear even weeks after a large dose. Rarely, hypersensitivity reactions have been reported. There has been suppression mainly of leukocytes and platelets in bone marrow.

In summary, the development of the *A,B,C,D* drugs represents a major advance in the treatment of neoplastic disease. However, in view of the numerous unusual toxicities, it is critical that physicians become familiar with these drugs and understand the necessary precautions in using them.

Summary

Four antineoplastic agents recently introduced —Adriamycin *(A)*, bleomycin *(B)*, CCNU *(C)* and DTIC *(D)*—are discussed with regard to unique toxicities, modes of action, administration, cost and types of neoplasms in which the drugs are most effective. It is hoped that this will serve as a guide for practitioners in their daily care of patients with cancer.

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Medical Information

Vulnerability to Disulfiram Psychosis

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ABBREVIATIONS USED IN TEXT

DA = dopamine
DBH = dopamine-beta-hydroxylase
NE = norepinephrine

DISULFIRAM (Antabuse) is a drug commonly used in the management of impulsive drinking in patients addicted to alcohol. Besides the severe cardiovasular effects it produces with alcohol intake (by increasing circulating acetaldehyde levels through inhibition of the enzyme aldehyde dehydrogenase), disulfiram has various adverse effects when used alone. These effects include drowsiness, fatigue, impotence, headaches, skin eruptions and polyneuritis, as well as, most seriously, neurological toxicity and psychosis. Disulfiram delirium is probably mediated by toxic metabolites, such as carbon disulfide (CS_2).[1] Nontoxic psychosis produced by disulfiram is frequently missed in clinical practice, as evidenced by the continued use of disulfiram in affected patients, or a diagnosis of psychosis that disregards the role of disulfiram in its precipitation.

In this paper, a hypothesis of vulnerability to disulfiram psychosis is proposed, based on the current lines of evidence for the biological mechanisms involved in the psychoses.

The Dopamine Hypothesis

The dopamine (DA) hypothesis of schizophrenia[2] states that an increase in DA activity in certain brain areas (probably the mesolimbic and mesocortical tracts) is associated with psychotic symptoms in schizophrenic patients. According to this hypothesis, drugs that increase DA activity (that is, DA agonists) would worsen the symptoms of schizophrenia, and this has been confirmed with controlled studies using amphetamine and methylphenidate (DA agonists) as well as L-dopa (a DA precursor). These drugs cause relapses in schizophrenic patients in doses much lower than those needed to produce psychosis in normal persons. On the other hand, DA antagonists such as neuroleptics (DA receptor blockers) produce a pronounced improvement or remission of schizophrenic symptoms, and alpha-methyl-para-tyrosine (a DA synthesis blocker) has been reported to potentiate the clinical efficacy of neuroleptics.

Disulfiram Is a DA Agonist

Disulfiram is an inhibitor of dopamine-beta-hydroxylase (DBH), an enzyme that catalyzes the metabolism of DA to norepinephrine (NE).[3] By inhibiting the metabolic pathway from DA to NE in the central nervous system, disulfiram results in an increase of DA concentrations. Therefore, disulfiram is a DA agonist, and is likely to exacerbate preexisting or latent psychosis, similar to amphetamine, methylphenidate and L-dopa.

DA and Affective Psychosis

Increased brain DA is highly correlated with psychomotor activity in animals, and L-dopa has been shown to produce episodes of hypomania and mania in most patients with bipolar affective psychosis.[4] It is possible, therefore, that disulfiram can uncover a preexisting or latent hypomania or mania.

Alcoholism, Affective Psychosis and Schizophrenia

Alcoholism was shown to occur more frequently in the first degree relatives of patients with manic-depressive psychosis, schizophrenia and al-

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coholism.[5] Schizophrenia and affective illness have also been shown to have a strong genetic component.[6,7] Therefore, alcohol addicts with family history of psychosis are likely to be more vulnerable to precipitants of psychosis than alcohol addicts without such history or than the general population.

DBH and Psychosis

Hartmann,[8] who proposes that a DBH deficit is the underlying mechanism of schizophrenia, describes in an experiment on himself how fusaric acid, a DBH inhibitor like disulfiram, did not have any effects on him except for some headache and stuffy nose. L-dopa alone had little effect on him as well. However, the combination of the two drugs produced in him a depersonalization syndrome, racing thoughts, unspecified fear bordering on terror and difficulty in sleeping. He suggests that the dopaminergic effects of L-dopa, in combination with DBH inhibiting effects of fusaric acid, recreate the biochemical disturbance in schizophrenia. Some evidence also is accumulating that certain subtypes of schizophrenia may have a DBH deficit while other subtypes do not.

A low activity of DBH in schizophrenia was also postulated by Wise and Stein,[9] who reported a deficit of this enzyme in the postmortem examinations of brains of schizophrenic patients. This finding was not replicated by Wyatt and coworkers[10] and measurements of DBH in serum of remitted or relapsed schizophrenic patients did not differ significantly from nonschizophrenic controls.[11] It is conceivable, however, that although DBH activity is not low in schizophrenic patients, a biochemical challenge with DBH inhibitors or DA agonists could induce a psychotic state.

In one study of the effects of disulfiram on serum DBH in 30 normal volunteers[12] one subject became psychotic while receiving 250 mg per day. He was found to have the lowest DBH activity in the group, and further history showed that he did have a schizophrenic episode a year before, which he had lied about.

DBH is also known to increase with stress,[13] apparently a physiological response necessary for the increased turnover of NE during stress. It is possible that DBH inhibition with disulfiram can compromise this adaptive response to stress, and increase the susceptibility to the increased DA activity that results from DBH inhibition.

The Literature on Disulfiram-Induced Psychosis

For many years after disulfiram was introduced in 1948, it was used in much higher doses (up to 2,000 mg per day) than it is now (125 to 500 mg per day). That resulted in many reports of toxicity, delirium and psychosis. Liddon and Satran[14] reviewed the literature on disulfiram psychosis and concluded that of 52 case reports in the literature, all but five were actually toxic delirium. Of these five patients, four had manic or hypomanic symptoms, and one had symptoms of paranoid schizophrenia. Many patients suffered from severe depression as well (which, according to the catecholamine hypothesis of depression, could be due to the blockage of NE synthesis by disulfiram's inhibition of DBH).

Heath and associates[15] reported that schizophrenic patients became worse and control subjects became toxic with the ingestion of large doses of disulfiram (1,500 mg per day for several days). There are no reported studies of the effects of low doses of disulfiram (125 to 250 mg per day) on schizophrenic symptoms.

Other reports in the literature indicate that patients with depression, schizoid personalities or borderline schizophrenia do poorly on regimens of disulfiram.[16,17]

Vulnerability to Disulfiram Psychosis

The following hypothesis is derived from the preceding discussion:

- Disulfiram, like amphetamine, L-dopa and and other DA agonists, can induce or exacerbate preexisting psychoses.
- Alcohol addicts with a history of drug-induced schizophrenic or affective psychosis are probably more vulnerable to disulfiram-induced psychosis than addicts with no such history.
- Alcohol addicts with a family history of psychosis (in parents, siblings or offspring) are probably more vulnerable than the general population to disulfiram-induced psychosis because of the assumed higher genetic predisposition to the biochemical correlates of psychosis, which may be uncovered by a disulfiram challenge.

The implications for the above are clear. Disulfiram should not be given indiscriminately to alcohol addicts, but only to those with no personal or family history of psychosis. For those with such history, disulfiram could induce or exacerbate a psychosis even at relatively low doses (250 to

500 mg per day). The author's clinical experience is compatible with this hypothesis but controlled studies to validate it are needed.

Conclusion

Disulfiram can produce psychosis, probably via its DBH inhibiting effects, which lead to an increase in DA activity. Because such an increase is associated with exacerbation of schizophrenic and affective psychosis (as with other DA agonists like amphetamine, L-dopa and methylphenidate) it is important to avoid using it in the management of alcohol addicts with a personal or family history of schizophrenia or manic-depressive psychosis.

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BOOK REVIEWS

THE WESTERN JOURNAL OF MEDICINE does not review all books sent to it by the publishers. A list of new books received is carried in the Advertising Section.

LET THE PATIENT DECIDE—A Doctor's Advice to Older Persons—Louis Shattuck Baer, MD. The Westminster Press, Withe - spoon Building, Philadelphia, PA (19107), 1978. 156 pages, $4.95 (Paperback).

This is not one of the recent flood of books concerned with the principles of death and dying, euthanasia, and the like. Rather, it is a practical guidebook, for older people, through the labyrinth of modern medical practice, by a general physician with some 30 years of primary care practice who draws on a number of clinical themes, all excitingly illustrated with real situations. As such the book is not aimed at physicians, but it is one that may be given to patients to study.

Dr. Baer draws his basic commitment from an observation of Jack London: "the proper function of man is to live—not to exist." He draws his thesis from a dictum of Epicurus: "the only human freedom is to choose or to avoid." And Dr. Baer, in no uncertain terms, exhorts his patients *to choose*. Even when death is inevitable, at least the how of death can be chosen. But only if the patient will grasp the opportunity and take the responsibility. The alternative is "to avoid." The author sets forth the all too familiar consequences of this action. In an exciting but devastating series of first hand anecdotes, he gives dramatic case histories from emergency rooms, coronary care units and nursing homes. This presentation is not a diatribe on these facilities but refers to the yin and yang of technical medicine, the bright and dark sides, acknowledging all the time the continuous pressure (legal, economic, political) on physicians and the management of the institutions. All through the book the emphasis is clear: without firm action on a patient's part, death, however friendly, will be warded off by the physician with every exotic means, and at whatever cost in money or the eventual quality of life or personal dignity.

In the latter part of the book the author projects for his readers the predictable ills they may fall heir to as they age—heart attacks, strokes, cancer and senility—and the probable action that will be taken *for* them in each case, if they do not anticipate and take charge.

The alternative options require a complete examination of the issues with family, friends, doctor and self. "What do you want from modern medicine and what don't you want? What are you willing to forego medically in order to avoid the simple prolongation of your existence?" This section contains a fine summary of the written instruments which have recently been developed to increase patients' autonomy: the living will, right-to-die legislation, patients' bills of rights, and the Medic Alert tags—all of these he recommends be considered before the final illness. In particular he urges his patients to look twice at all *routine* "conditions of admission" forms and not to take anything for granted (especially for hospitals and nursing homes) and also at the standard surgeon's and anesthetist's permit forms. He urges not only to look twice, but actually *to alter* these forms in writing to conform to one's own wishes and beliefs. He recognizes the probable reactions to such actions, but reiterates his continuing theme: it is time for the patient to give instructions about his or her own wishes. So the message of the book comes through loudly and clearly: be active. A physician or sophisticated reader may find the book oversimplified and repetitive. But to the "older persons" to whom it is addessed, if forewarned is forearmed, Dr. Baer has performed a valuable service. It deserves a place in physicians' libraries among those other books that are given to patients to help them achieve understanding.

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* * *

FEMALE SEXUALITY FOLLOWING SPINAL CORD INJURY—Elle Friedman Becker. Accent Special Publications, Cheever Publishing, Inc., P.O. Box 700, Bloomington, IL (61701), 1978. 273 pages, spiral bound, $10.95. Shipped postage paid from Ms Elle Friedman Becker, 1571 Alvarado Ave., No. 1, Walnut Creek, CA 94596.

The author of this book, who sustained a spinal injury at the level of T-6 as a result of being thrown from her horse, found during her hospital stay and rehabilitation that there was an abysmal lack of knowledge available concerning the subject of female sexuality following spinal cord injuries. This book represents her research into this subject and will provide a great deal of insight into the problems faced by not only the author but a number of women whom she interviewed during the preparation of this book.

This book has been written primarily for women who are either paraplegic or quadriplegic to provide them with information about the physical, medical and emotional aspects of spinal cord injury. It also discusses such problems as bladder and bowel problems, the use of catheters, birth control techniques and how a group of women have solved these and other problems, both in relationship to their self-image and their sexuality. However, the book also should be helpful to physicians and other health professionals because it gives an insight into how such patients view the medical profession and what they expect from health professionals.

The book is in the form of questions and answers, except for a chapter detailing the anatomy of the spinal cord. Included in the book are interviews with a physician who specializes in marriage and family counseling, a physiatrist, a neurologist, a urologist, a clinical psychologist, a psychiatrist, a vocational rehabilitation counselor, a physical therapist, an instructor in female sexuality and 15 paraplegic or quadriplegic women.

The interview technique has one drawback: when the spoken word is set down in writing, it sometimes loses clarity. Some passages in the book, therefore, require a second reading to be sure of the speaker's intent. The plastic spiral type of binding used was somewhat troublesome for this reader, but because the book lies flat when opened this type of binding allows independent reading by paraplegic or quadriplegic persons. Several spelling mistakes could be confusing to the uninitiated, but will cause no problem to more sophisticated readers.

An excellent glossary of medical and other terms used in the book is included, as well as an extensive bibliography.

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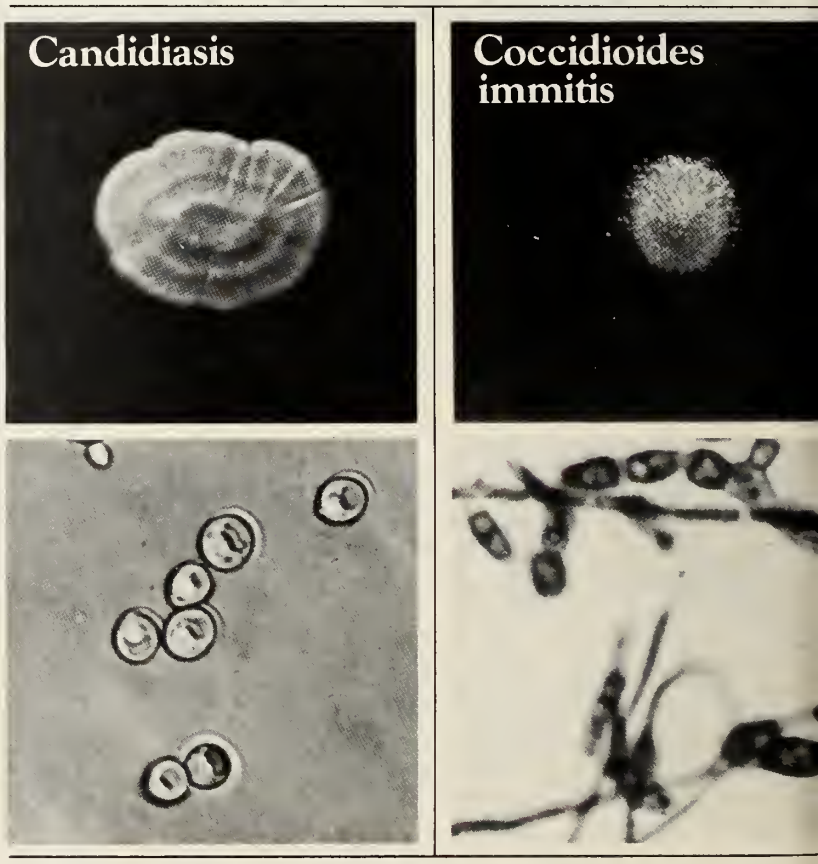

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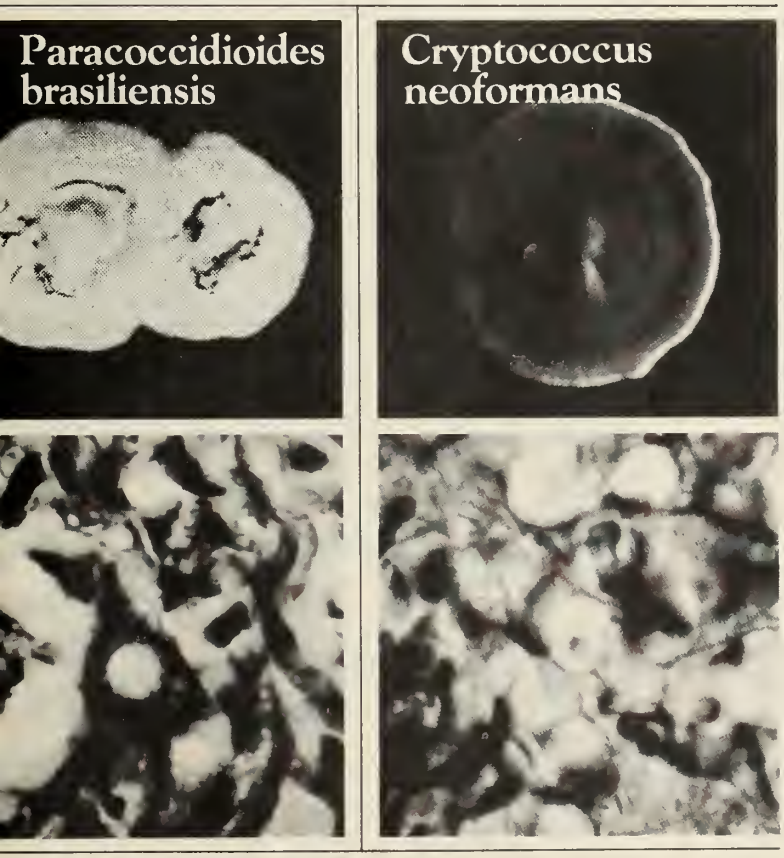

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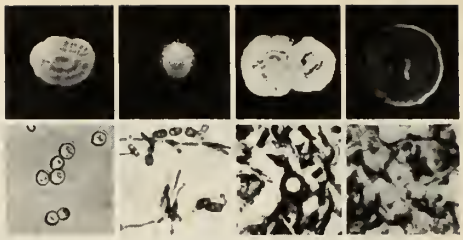

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CONTRAINDICATIONS: MONISTAT i.v. is contraindicated in those patients who have shown hypersensitivity to it.

WARNINGS: Rapid injection of undiluted MONISTAT i.v., may produce transient tachycardia or arrhythmia

PRECAUTIONS: Before a treatment course of MONISTAT i.v. is started, the physician should make sure that the patient is not hypersensitive to the drug product. MONISTAT i.v. should be given by intravenous infusion. The treatment should be started under stringent conditions of hospitalization but subsequently may be given to suitable patients under ambulatory conditions with close clinical monitoring. It is recommended that an initial dose of 200 mg be given with the physician in attendance. It is also recommended that clinical laboratory monitoring including hemoglobin, hematocrit, electrolytes and lipids be performed.

It should be borne in mind that systemic fungal mycoses may be complications of chronic underlying conditions which in themselves may require appropriate measures.

Pregnancy: Reproductive studies with MONISTAT i.v. in rats and rabbits revealed no evidence of impaired fertility or harm to the fetus. There are no data, however, on the use of the drug in pregnant women.

Children: Since the safety of miconazole i.v. in children under one year of age has not been extensively studied, its benefits in this age group must be weighed against the possible risks involved.

ADVERSE REACTIONS: Adverse reactions which have been observed with MONISTAT i.v. therapy include phlebitis, pruritus, rash, nausea, vomiting, febrile reactions, drowsiness, diarrhea, anorexia and flushes. In the U.S. studies, 29% of 209 patients studied had phlebitis, 21% pruritus, 18% nausea, 10% fever and chills, 9% rash, and 7% emesis. Transient decreases in hematocrit and serum sodium values have been observed following infusion of MONISTAT i.v. Thrombocytopenia has also been reported. No serious renal or hepatic toxicity has been reported. If pruritus and skin rashes are severe, discontinuation of treatment may be necessary. Nausea and vomiting can be mitigated with antihistaminic or antiemetic drugs given prior to MONISTAT i.v. infusion, or by reducing the dose, slowing the rate of infusion, or avoiding administration at mealtime.

Aggregation of erythrocytes or rouleau formation on blood smears has been reported. Hyperlipemia has occurred in patients and is reported to be due to the vehicle, Cremophor EL (PEG 40 castor oil).

DRUG INTERACTIONS: Drugs containing cremophor-type vehicles are known to cause electrophoretic abnormalities of the lipoprotein. These effects are reversible upon discontinuation of treatment but are usually not an indication that treatment should be discontinued.

Interaction with the coumarin drugs resulting in an enhancement of the anticoagulant effect has also been reported. In cases of simultaneous treatment with MONISTAT i.v. and coumarin drugs, the anticoagulant effect should be carefully titrated since reductions of the anticoagulant doses may be indicated.

DOSAGE AND ADMINISTRATION

DOSAGE

Adults. The doses may vary with the diagnosis and with the infective agent, from 200 to 1200 mg per infusion. The following daily doses, which may be divided over 3 infusions, are recommended:

Organism	Dosage Range*	Duration of Successful Therapy (weeks)
Coccidioidomycosis:	1800 to 3600 mg per day	3 to > 20
Cryptococcosis:	1200 to 2400 mg per day	3 to > 12
Candidiasis:	600 to 1800 mg per day	1 to > 20
Paracoccidioidomycosis:	200 to 1200 mg per day	2 to > 16

*May be divioed over 3 infusions.

Repeated courses may be necessitated by relapse or reinfection.

Children: A total daily dose of about 20 to 40 mg/kg is generally adequate. However, a dose of 15 mg/kg body weight per infusion should not be exceeded.

ADMINISTRATION: MONISTAT i.v. should be diluted in at least 200 ml of fluid. The diluent of choice is 0.9% sodium chloride or alternatively Dextrose 5% injectable solution. The intravenous infusion should be given over a period of 30 to 60 minutes.

Generally, treatment should be continued until all clinical and laboratory tests no longer indicate that active fungal infection is present. Inadequate periods of treatment may yield poor response and lead to early recurrence of clinical symptoms. The dosing intervals and sites and the duration of treatment vary from patient to patient and depend on the causative organism.

OTHER MODES OF ADMINISTRATION: Intrathecal. Administration of the undiluted injectable solution of MONISTAT i.v. by the various intrathecal routes (20 mg per dose) is indicated as an adjunct to intravenous treatment in fungal meningitis. Succeeding intrathecal injections may be alternated between lumbar, cervical, and cisternal punctures every 3 to 7 days. Bladder instillation of 200 mg of diluted solution is indicated in the treatment of mycoses of the urinary bladder.

HOW SUPPLIED: MONISTAT i.v. is supplied in 20 ml ampoules.

MONISTAT i.v. (miconazole) is an original product of Janssen Pharmaceutica N.V., Belgium, and co-developed by Ortho Pharmaceutical Corporation.

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WJ6/79

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tober 1978

BOOKS RECEIVED

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

CANCER RESEARCH SINCE 1900—An Evaluation—Sigismund Peller, MD. Philosophical Library Inc., 15 East 40 Street, New York City (10016), 1979. 394 pages, $15.00.

INHERITED DISORDERS OF THE SKELETON—Peter Beighton, MD, PhD, FRCP(Ed), DCH, Professor of Human Genetics, University of Cape Town, Consultant in Medical Genetics, Groote Schuur Hospital, Cape Town, South Africa—in the series GENETICS IN MEDICINE AND SURGERY—General Editor: Allan E. H. Emery, MD, PhD, DSc, FRCP(E), MFCM, FRS(E), Professor of Human Genetics, University of Edinburgh. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York (10036), 1978. 267 pages, $38.00.

JEAN'S WAY—Derek Humphrey with Ann Wickett. Quartet Books Inc., New York City (10021), 1978. 116 pages, $8.95; distributed by Horizon Press Publishers, 156 Fifth Avenue, New York City 10010.

THE PARENTS' GUIDE TO CHILD RAISING—Editor: Glenn Austin, MD, pediatrician in private practice, Los Altos, California; Associate Editors: Julia Stone Oliver and John C. Richards, MD. Prentice-Hall, Inc., Englewood Cliffs, NJ (07632), 1978. 374 pages, $15.95 (Hard cover), $7.95 (Soft cover).

PHYSICIAN'S HANDBOOK—Nineteenth Edition—Marcus A. Krupp, MD, Clinical Professor of Medicine, Stanford University School of Medicine, Director of Research, Palo Alto Medical Research Foundation, Director of Laboratories, Palo Alto Medical Clinic; Norman J. Sweet, MD, Emeritus Professor of Medicine, University of California, San Francisco, Family Health Program, Long Beach; Ernest Jawetz, MD, PhD, Professor of Microbiology and Medicine, University of California, San Francisco; Edward G. Biglieri, MD, Professor of Medicine, Chief of Endocrine Services, San Francisco General Hospital, University of California, San Francisco; Robert L. Roe, MD, Associate Professor of Medicine, University of California, San Francisco; and Carlos A. Camargo, MD, Associate Professor of Clinical Medicine, Stanford, Director of Endocrine Clinic, Stanford University Hospital. Lange Medical Publications, Drawer L, Los Altos, CA (94022), 1979. 758 pages, $9.00.

PROGRESS IN CLINICAL MEDICINE—Seventh Edition—Edited by A. R. Horler, MD, FRCP, Physician, Royal Victoria Infirmary, Newcastle upon Tyne; and J. B. Foster, MD, FRCP, Neurologist, Regional Neurological Centre, Newcastle upon Tyne. Churchill Livingstone—Medical Division of Longman Inc., 19 West 44th St., New York City (10036), 1978. 485 pages, $38.00.

RECENT ADVANCES IN ENDOCRINOLOGY AND METABOLISM—Number 1—Edited by J. L. H. O'Riordan, DM, FRCP, Senior Lecturer in Medicine and Honorary Consultant Physician, The Middlesex Hospital, London. Churchill Livingstone—Medical Division of Longman, Inc., 19 West 44th St., New York City (10036), 1978. 282 pages, $27.50.

RESPIRATORY FUNCTION OF THE LUNG AND ITS CONTROL—Fred S. Grodins, MD, PhD, Professor and Chairman, Department of Biomedical Engineering, and Professor of Physiology; and Stanley M. Yamashiro, PhD, Associate Professor of Biomedical Engineering, University of Southern California, Los Angeles—in the series: **MODERN CONCEPTS IN MEDICAL PHYSIOLOGY**—Lysle H. Peterson, MD, Consulting Editor. Macmillan Publishing Co., Inc., 866 Third Avenue, New York City (10022), 1978. 148 pages, $13.50 (cloth), $9.95 (Paperback).

THYROID CANCER—Editor: Larry D. Greenfield, MD, Director, Department of Nuclear Medicine, Co-Director, Thyroid Oncology Service, Radiation Oncologist, City of Hope National Medical Center, Duarte, California. CRC Press, Inc., 2255 Palm Beach Lakes Blvd., West Palm Beach, FL (33409), 1978. 267 pages, $64.95, outside U.S. $74.95.

TWIN RESEARCH: Part A—Psychology and Methodology; Part B—Biology and Epidemiology; Part C—Clinical Studies—Volumes 24A, 24B and 24C in the series PROGRESS IN CLINICAL AND BIOLOGICAL RESEARCH—Editor Walter E. Nance; Associate Editors: Gordon Allen and Paolo Parisi. Alan R. Liss, Inc., 150 Fifth Ave., New York City (10011), 1978. 3 volume set, $80.00; Part A, 284 pages, $28.00; Part B, 222 pages, $22.00; Part C, 296 pages, $30.00.

UP AND AROUND—Rehabilitation Exercises for Cancer Patients—Second Edition, Revised—Ernest H. Rosenbaum, MD; Francine Manuel, RPT; Judith Bray, OTR; Isadora R. Rosenbaum, and Arthur Z. Cerf, MD. Exercises demonstrated by Jack LaLanne. Life, Mind & Body, 1515 Scott St., San Francisco (94115), 1978. 45 pages, $3.00 (Paperback).

USES OF ENZYMES AND IMMOBILIZED ENZYMES—Francis X. Hasselberger, PhD. Nelson-Hall Publishers, 325 W. Jackson Blvd., Chicago (60606), 1978. 220 pages, $14.95.

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SURGICAL HOUSE OFFICER—Part-time pre and post op care. Small private San Francisco hospital. Direct inquiry to Dr. Alan Rosenstein, (415) 386-7000.

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BOARD CERTIFIED INTERNISTS needed for salaried positions as primary care practitioners with San Francisco Bay Area pre-paid Health Plan. Excellent benefits. Outstanding opportunity for qualified persons. Send C.V. to Box 6034, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103. Equal opportunity employer.

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(Continued on Page 30)

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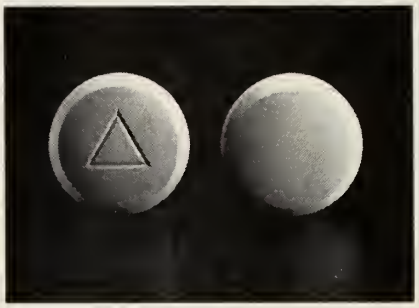
The Maker

Examining a Few Myths About Prescribing.



Increasing pressure is being put on the practicing physician to prescribe drugs generically. You are told that brand-name products are universally "expensive" and generic versions are relatively "cheap." To make this case, the most extreme (rather than typical) price differentials are cited. Thus, consumers are led to believe that such differentials are commonplace. Even your knowledge and your motives as a physician are questioned.

Understandably, these views have created myths. We think it's time to examine them in the light of all the facts and ramifications.

MYTH: There are no differences in quality and performance between brand-name products and their generic counterparts. The corollary is that there are no differences among products made by high-technology, quality-conscious, research-based companies and those made by commodity-type suppliers.

FACT: The Food and Drug Administration does a good job in monitoring a generally excellent drug supply. Still, it has nowhere near the resources to guarantee the quality and bioavailability of all marketed products at any given time. Just a few months ago, for example, it noted that batches of tetracycline HCl capsules which met official monograph requirements were not bioequivalent to a reference product. As you know, there is substantial literature on this subject affecting many drugs, including such antibiotics as tetracycline and erythromycin. The record on drug recalls and court actions affirms strongly that there are differences among pharmaceutical companies and their products. Research-intensive companies have far better records than those that do no research and may practice minimum quality assurance.

MYTH: Industry favors only "expensive" brand names and denigrates all generics.

FACT: PMA companies make 90 to 95 percent of the drug supply, including, therefore, most of the generics. Drug nomenclature is not the important point; it's the competence of the manufacturer and the integrity of the product that count.

Matters.

MYTH: Generic options almost always exist.

FACT: About 55 percent of prescription drug expenditure is for single-source drugs. This means, of course, that for only 45 percent of such expenditure, is a generic prescribing option available.

MYTH: Generic prescriptions are filled with inexpensive generics, thus saving consumers large sums of money.

FACT: Market data show that you invariably prescribe—and pharmacists dispense—both brand and generically labeled products from known and trusted sources, in the best interest of patients. In most cases the patient receives a proven brand product. Savings from voluntary or mandated generic prescribing are grossly exaggerated.

MYTH: Drugs account for a major portion of the rise in health care costs.

FACT: Drugs represent a very small part of such costs. The amount of the health care dollar spent for prescription drugs was about 12 cents in 1967; today it is about 8 cents. And you as a physician are most conscious of how drug therapy can cut hospitalization, avert surgery, reduce office visits and keep patients on the job.

MYTH: Government intrusions into the marketplace will save tax money.

FACT: Government schemes always cost the taxpayer something, and the costs often exceed the benefits. Certainly, any federal "help," such as lists of wholesale drug prices sent to all physicians and pharmacists, will be no exception. Just think of the expense of keeping them current! Moreover, wholesale prices are poor guides to actual transaction prices and even worse guides to retail prices.

The PMA Position

We believe your freedom to prescribe, either by generic or brand name, should be totally unabridged. Otherwise, your prescribing prerogatives and your relationships with patients will be seriously impaired.

The maker does matter

After the myths about price and equivalency have been shattered, one fact stands out more clearly than ever: *The maker does matter.* As always, your best guide to drug therapy for your patients is to select products—both brands and generics—from manufacturers with credentials and performance records you have come to respect.

PMA

Pharmaceutical Manufacturers Association
1155 Fifteenth Street, N.W.
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(Continued from Page 26)

PHYSICIANS WANTED

SEATTLE—UROLOGY. Group Health Cooperative of Puget Sound is seeking board certified/eligible applicants for a vacancy in our 6 person urology department. The urology group provides referral-only urologic care to our Plan's 260,000 Puget Sound members. Contact Bill Rollins, MD, GHC, 200 15th Ave. E., Seattle 98112. EOE

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INTERNIST: Board Certified or eligible internist with subspecialty in pulmonary disease sought by multispecialty group. Guaranteed salary or percentage basis. Easy access to community hospitals. Easy driving distance to UCLA and USC Medical Schools. Contact: Victor W. Gieschen, MD, 2230 Lynn Road, Thousand Oaks, CA 91360. Phone (805) 495-1066.

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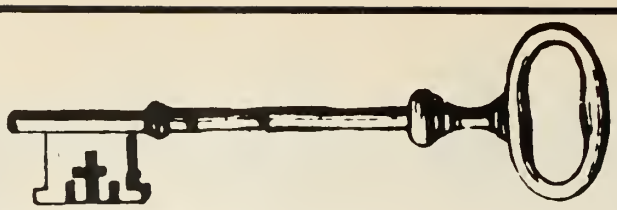

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(Continued on Page 32)

FAMILY PRACTICE

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COURSE DESCRIPTION

This course offers a comprehensive technical program for the care of the critically ill patient in the Emergency Department.

The program is designed for the practicing emergency physician and/or primary care physician who sees occasional major trauma. The care of the critically ill patient, including resuscitation, diagnostic modalities, and initial management will be covered.

The course is clinically oriented; it will cover in detail technical skills required to treat injuries of the thorax and abdomen, but the curriculum also includes commonly seen neurological and orthopedic abnormalities, as well as instruction in regional block anesthesia.

There will be laboratories on each day of the course which will allow participants a chance to polish technical skills required to manage the critically ill or injured patient. These laboratories will be administered by physicians whose primary field of interest is Emergency Medicine.

Upon completion of this course, registrants should become more competent in the performing of technical skills required in the management of critically ill patients.

PROGRAM HIGHLIGHTS

- **LECTURES: 8 a.m.-12 noon**

Resuscitation of the Trauma Patient; Peritoneal Lavage; Pericardiocentesis; Crico-Thyroid Cannulation; Miscellaneous Emergency Airway Techniques; Placement of Long-Line, Widebore and CVP Catheters; Regional Anesthesia (including Dental); Thoractomy—open and closed; Neurosurgical Emergencies; Aspiration and Injection of Inflamed Joints.

- **LABORATORY: 2 p.m.-6 p.m.**
  Dog Lab:

Chest Tube Placement; Tracheal Intubation; Pericardiocentesis; Long-line Placement—Percutaneous; Long-line Placement—Cut Down; Trans-Tracheal Aeration; Crico-Thyroid Cannulation; Peritoneal Lavage; CVP Placement and Readings; Open Thoracotomy; Aortic Cross-Clamping; Pacemaker Insertion.

- **Suture Lab**

Each registrant will have an opportunity to practice various suture techniques under the instruction of Plastic Surgeons.

- **Miscellaneous Lab:** (cadaver and/or student subjects)

E. D. Spirometry; MAST Trousers Application; Fiberotic Laryngoscopy; Indirect Laryngoscopy; Filiforms, Followers, Dilators, Specialized Catheters; Post Nasal Packs; Chest Tube Insertion; Splinting; Doppler Technique.

PROGRAM COORDINATORS

DAVID I. GREENLY, MD

Clinical Instructor Surgery; Attending Staff—Mission Emergency Hospital, San Francisco General Hospital Medical Center; Emergency Services Medical Group, Alta Bates Hospital, Berkeley, California.

WILLIAM L. TEUFEL, MD

Assistant Clinical Professor of Surgery, University of California School of Medicine, San Francisco; Director, Mission Emergency Hospital, San Francisco General Hospital Medical Center, San Francisco.

PARTIAL FACULTY LIST

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CREDITS

Application for 23 hours Category I credit has been submitted to ACEP. We do not foresee any difficulties with approval as last year's course was approved without delay. This seminar is approved for up to 24 hours formal Category I CME credits, CMA/AMA and for prescribed hours for AAFP.

ACCOMMODATIONS: A block of rooms has been reserved at the Holiday Inn—Fisherman's Wharf. A room reservation card will be sent to you with your course confirmation. Bus service to the hospital will be provided.

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Alta Bates Hospital, 3001 Colby Street at Webster, Berkeley, CA 94705

(Continued from Page 30)

PHYSICIANS WANTED

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PATHOLOGIST—37, AP-CP, California License. Wishes to relocate in Southern California; Hospital-Besed or Group Practice Preferred; Available Fall 1979. Write Box 6049, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

ASSOCIATE MEDICAL DIRECTOR of major insurance company seeks relocation to the West Coast. Write Box 6048, Western Journal of Medicine, 731 Market St., San Francisco, CA 94103.

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Adverse Reactions: Hypersensitivity, including fatal anaphylaxis. Nausea, vomiting, epigastric distress, diarrhea, and black, hairy tongue. Skin eruptions, urticaria, reactions resembling serum sickness (including chills, edema, arthralgia, prostration), laryngeal edema, fever, and eosinophilia. Infrequent hemolytic anemia, leukopenia, thrombocytopenia, neuropathy, and nephropathy, usually with high doses of parenteral penicillin. [102175]

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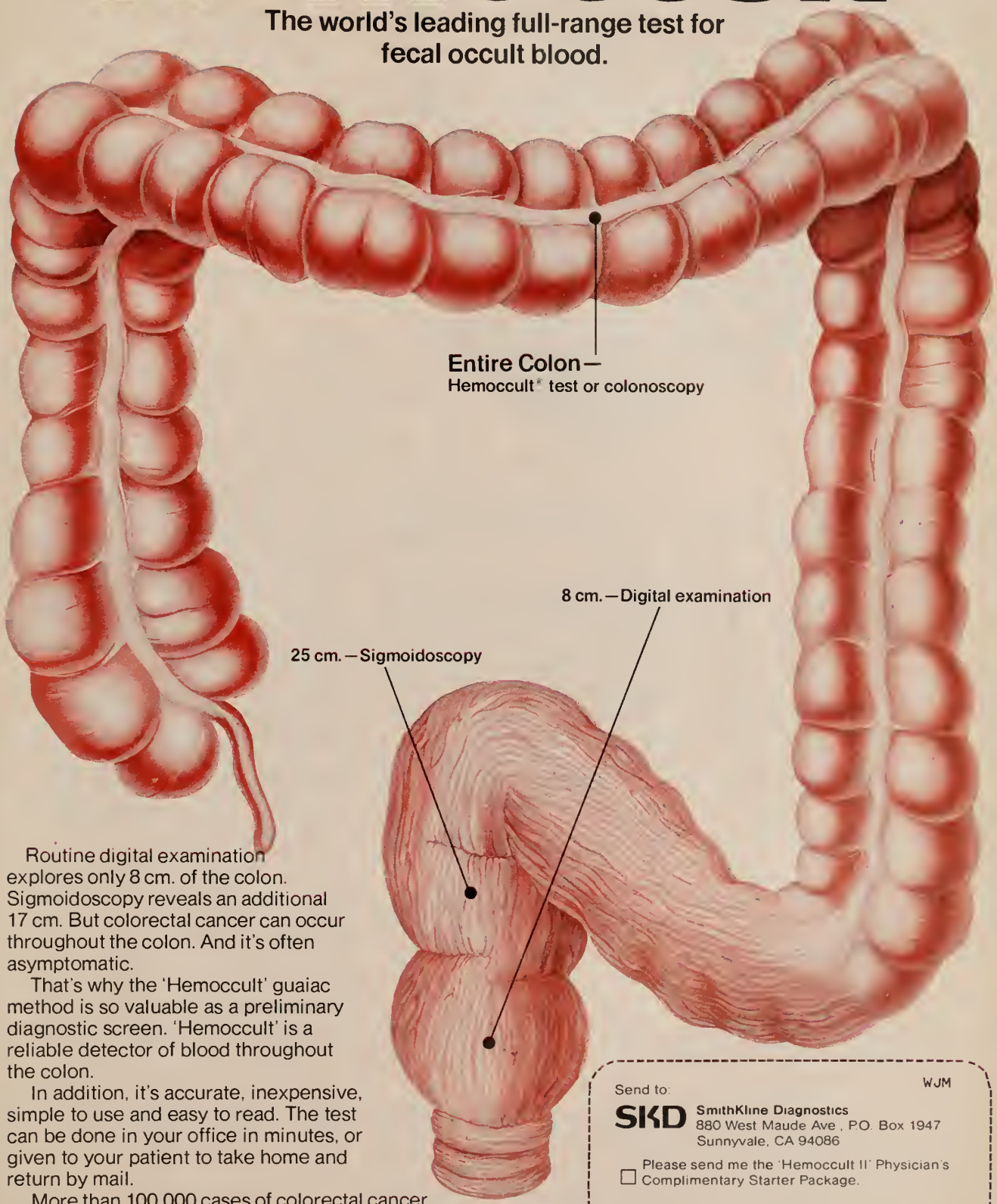

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INDICATIONS AND USE: This is not an innocuous drug and strict attention should be given to the indications for its use. Pending further investigation, its use in other hyperuricemic states is not indicated at this time.

Zyloprim® (allopurinol) is intended for:

1. treatment of gout, either primary, or secondary to the hyperuricemia associated with blood dyscrasias and their therapy;
2. treatment of primary or secondary uric acid nephropathy, with or without accompanying symptoms of gout;
3. treatment of patients with recurrent uric acid stone formation;
4. prophylactic treatment to prevent tissue urate deposition, renal calculi, or uric acid nephropathy in patients with leukemias, lymphomas and malignancies who are receiving cancer chemotherapy with its resultant elevating effect on serum uric acid levels.

CONTRAINDICATIONS: Use in children with the exception of those with hyperuricemia secondary to malignancy. The drug should not be employed in nursing mothers.

Patients who have developed a severe reaction to Zyloprim should not be restarted on the drug.

WARNINGS: ZYLOPRIM SHOULD BE DISCONTINUED AT THE FIRST APPEARANCE OF SKIN RASH OR ANY SIGN OF ADVERSE REACTION. In some instances a skin rash may be followed by more severe hypersensitivity reactions such as exfoliative, urticarial and purpuric lesions as well as Stevens-Johnson syndrome (erythema multiforme) and very rarely a generalized vasculitis which may lead to irreversible hepatotoxicity and death.

A few cases of reversible clinical hepatotoxicity have been noted and in some patients asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed. Accordingly, periodic liver function tests should be performed during the early stages of therapy, particularly in patients with pre-existing liver disease.

Patients should be alerted to the need for due precautions when engaging in activities where alertness is mandatory.

Nevertheless, iron salts should not be given simultaneously with Zyloprim. This drug should not be administered to immediate relatives of patients with idiopathic hemochromatosis.

In patients receiving Purinethol® (mercaptopurine) or Imuran® (azathioprine), the concomitant administration of 300-600 mg of Zyloprim per day will require a reduction in dose to approximately one-third to one-fourth of the usual dose of mercaptopurine or azathioprine. Subsequent adjustment of doses of Purinethol or Imuran should be made on the basis of therapeutic response and any toxic effects.

Usage in Pregnancy and Women of Childbearing Age: Zyloprim® (allopurinol) should be used in pregnant women or women of childbearing age only if the potential benefits to the patient are weighed against the possible risk to the fetus.

PRECAUTIONS: Some investigators have reported an increase in acute attacks of gout during the early stages of allopurinol administration, even when normal or subnormal serum uric acid levels have been attained.

It has been reported that allopurinol prolongs the half-life of the anticoagulant, dicumarol. This interaction should be kept in mind when allopurinol is given to patients already on anticoagulant therapy, and the coagulation time should be reassessed.

A fluid intake sufficient to yield a daily urinary output of at least 2 liters and the maintenance of a neutral or, preferably, slightly alkaline urine are desirable to (1) avoid the theoretic possibility of formation of xanthine calculi under the influence of Zyloprim therapy and (2) help prevent renal precipitation of urates in patients receiving concomitant uricosuric agents.

Patients with impaired renal function require less drug and should be carefully observed during the early stages of Zyloprim administration and the drug withdrawn if increased abnormalities in renal function appear.

In patients with severely impaired renal function, or decreased urate clearance, the half-life of oxipurinol in the plasma is greatly prolonged. Therefore, a dose of 100 mg per day or 300 mg twice a week, or perhaps less, may be sufficient to maintain adequate xanthine oxidase inhibition to reduce serum urate levels. Such patients should be treated with the lowest effective dose, in order to minimize side effects.

Mild reticulocytosis has appeared in some patients.

As with all new agents, periodic determination of liver and kidney function and complete blood counts should be performed especially during the first few months of therapy.

ADVERSE REACTIONS:

Dermatologic: Because in some instances skin rash has been followed by severe hypersensitivity reactions, it is recommended that therapy be discontinued at the first sign of rash or other adverse reaction (see WARNINGS). Skin rash, usually maculopapular, is the adverse reaction most commonly reported.
Exfoliative, urticarial and purpuric lesions, Stevens-Johnson syndrome (erythema multiforme) and toxic epidermal necrolysis have also been reported.
A few cases of alopecia with and without accompanying dermatitis have been reported.
In some patients with a rash, restarting Zyloprim (allopurinol) therapy at lower doses has been accomplished without untoward incident.

Gastrointestinal: Nausea, vomiting, diarrhea, and intermittent abdominal pain have been reported.

Vascular: There have been rare instances of a generalized hypersensitivity vasculitis or necrotizing angiitis which have led to irreversible hepatotoxicity and death.

Hematopoietic: Agranulocytosis, anemia, aplastic anemia, bone marrow depression, leukopenia, pancytopenia and thrombocytopenia have been reported in patients, most of whom received concomitant drugs with potential for causing these reactions. Zyloprim® (allopurinol) has been neither implicated nor excluded as a cause of these reactions.

Neurologic: There have been a few reports of peripheral neuritis occurring while patients were taking Zyloprim. Drowsiness has also been reported in a few patients.

Ophthalmic: There have been a few reports of cataracts found in patients receiving Zyloprim. It is not known if the cataracts predated the Zyloprim therapy. "Toxic" cataracts were reported in one patient who also received an anti-inflammatory agent; again, the time of onset is unknown. In a group of patients followed by Gutman and Yü for up to five years on Zyloprim therapy, no evidence of ophthalmologic effect attributable to Zyloprim was reported.

Drug Idiosyncrasy: Symptoms suggestive of drug idiosyncrasy have been reported in a few patients. This was characterized by fever, chills, leukopenia or leukocytosis, eosinophilia, arthralgias, skin rash, pruritus, nausea and vomiting.

OVERDOSAGE: Massive overdosing, or acute poisoning, by Zyloprim has not been reported.

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ANESTHESIOLOGY

June 22-24—**Practical Closed System Anesthesia.** PMC. Friday-Sunday.

August 4—**Obstetrical Anesthesia.** Mercy Hospital and Medical Center, San Diego. Saturday. Contact: Gilbert E. Kinyon, MD, Dir. of Anesthesia, Mercy Hospital & Medical Center, 4077 Fifth Ave., San Diego 92103. (714) 294-8037.

September 15-22—**Practical Management of Anesthetic Problems.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 31½ hrs. $325.

October 20-24—**American Society of Anesthesiologists—Annual Meeting.** San Francisco. Saturday-Wednesday. Contact: William S. Marinko, Asst. Exec. Sec., ASA, 515 Busse Highway, Park Ridge, IL 60068. (312) 825-5586.

October 25-November 2—**Post ASA Hawaiian Seminar.** Kona Village Resort, Hawaii. 9 days. 28 hrs. Contact: Adham Safwat, Box 7550, Menlo Park 94025. (415) 494-3799.

CANCER

June 18-22—**Head and Neck Oncology.** UCLA. Monday-Friday. 35 hrs. $400.

July 13-14—**Oncology Symposium.** Area Health Education Center, UCSF, at Del Monte Hyatt, Monterey. Friday-Saturday. Contact: Remi Barron, Area Health Education Ctr., P.O. Box 1611, Salinas 93902. (408) 757-3616.

August 1-5—**20th Annual Advanced Seminars in Dermatology (Current Topics in Cancer)—Malignant Melanoma and Lymphoma.** See Medicine, August 1-5.

September 20-22—**Bladder Cancer.** American Urological Assn. at Hilton Hotel, San Diego. Thursday-Saturday. 16 hrs. $200, members; $250, nonmembers. Contact: Mary Rohan, AUA Office of Education, P.O. Box 1129, Aspen, CO 81611. (303) 925-2012.

September 26—**Head and Neck Cancer Symposium.** Hospital of the Good Samaritan, Los Angeles. Wednesday. 7 hrs. Contact: Janie Sternal, CME Coordinator, 616 S. Witmer St., Los Angeles 90017. (213) 488-8123.

October 20—**Lung Cancer.** San Francisco Regional Cancer Foundation at Fireman's Fund Building, San Francisco. Saturday. 4 hrs. Contact: Norma Schlager, PhD, S.F. Regional Cancer Foundation, 14th and Lake, San Francisco 94118. (415) 221-2132.

EMERGENCY MEDICINE

June 16—**Abdominal Injuries.** DREW at New Otani Hotel and Garden, Los Angeles. Saturday. 8 hrs. Contact: S. Balasubramaniam, MD, Acting Dir. of Emergency Services, DREW.

June 18-22—**Advanced Emergency Medicine.** STAN. Monday-Friday. 25 hrs. $290.

June 20-22—**Symposium on Emergency Room Radiology.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Thursday. 16 hrs. $160.

June 25-29—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 40 hrs. $350.

August 13-17—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD. Monday-Friday. 43 hrs. $350.

September 8—**Orange County Emergency Workshop Part III—Neurological Trauma.** UCI. Saturday. 5 hrs.

September 24—**Trauma—Auto and Motorcycle Patients.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

September 24-28—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Hilton Hotel, San Diego. Monday-Friday. 43 hrs. $350.

October 8-12—**Postgraduate Institute for Emergency Physicians, Symposium III.** UCSD at Vacation Village, San Diego. Monday-Friday. 43 hrs. $350.

MEDICINE

June 15-16—**Recent Advances in Pheresis.** PMC at St. Francis Hotel, San Francisco. Friday-Saturday. 12 hrs.

June 15-July 28—**Summer Gerontology Institute.** See Of Interest To All, June 15-July 28.

June 18—**Crohn's Disease.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

KEY TO ABBREVIATIONS AND SYMBOLS

Medical Centers and CMA Contacts for Information

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 731 Market Street, San Francisco 94103. (415) 777-2000.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Duane Dillman, PhD, Director, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3091.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, Ext. 2400.

PMC: Pacific Medical Center
Contact: Martin Brotman, MD, Chairman, Education Committee, Pacific Medical Center, P.O. Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Neil C. Andrews, MD, Chairman, Department of Postgraduate Medicine, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, California College of Medicine, Irvine
Contact: Robert Combs, MD, Associate Dean, Continuing Medical Education, University of California, Irvine—California College of Medicine, Irvine 92717 (714) 833-5991.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, P.O. Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: David Allan, MD, Associate Dean for Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (714) 452-3708.

UCSF: University of California, San Francisco
Contact: Malcolm S. M. Watts, MD, Associate Dean and Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 226-2047.

June 20-22—**Pediatric Gastroenterology.** See Pediatrics, June 20-22.

June 27-29—**Hepatobiliary Disease in Clinical Practice.** PMC at Holiday Inn on Union Square, San Francisco. Wednesday-Friday. 15 hrs. $180.

July 13-15—**Cardiac Symptoms, Arrhythmias and Holter Monitoring.** International Medical Education Corp. at Hyatt, Anaheim. Friday-Sunday. 13 hrs. $215. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

July 19-20—**New Approaches to Immunosuppression.** PMC at Fairmont Hotel, San Francisco. Thursday-Friday. 12 hrs. $100.

July 23—**Management of Diabetes.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

July 23-24—**Microcirculatory Approach to Current Medical and Surgical Problems.** Microcirculatory Society and American Heart Assn., Greater Los Angeles Affiliate, at Hilton, San Diego. Monday-Tuesday. 14 hrs. $175, before April 1; $200, thereafter. Contact: Nomi Feldman, Conf. Coordinator, 2321 Morena Blvd., San Diego 92110. (714) 275-0650.

July 27-29—**EKG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Doubletree Inn, Monterey. Friday-Sunday. 15 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

July 27-30—**Medical Mycology-Dermatomycology—4th Annual Course.** Memorial Hospital Medical Center-UCI Center for Health Education at Sheraton-Newport, Newport Beach. Friday-Monday. 36 hrs. $300. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

July 30-August 3—**Endocrinology and Metabolism.** UCSF at Hyatt Regency, San Francisco. Monday-Friday.

August 1-5—**20th Annual Seminars in Dermatology (Current Topics in Cancer)—Malignant Melanoma and Lymphoma.** Memorial Hosp. Med. Ctr.-UCI Ctr. for Health Education at Sheraton-Newport, Newport Beach. 14 hrs. $175. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

August 4—**Pediatric Dermatology Seminar.** STAN. Saturday. 7 hrs. $75. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

August 16-18—**Podiatric Dermatology Symposium.** STAN. Thursday-Saturday. 17 hrs. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford Univ. Sch. of Med., Stanford 94305. (415) 497-6101.

August 27-31—**Update in Internal Medicine.** Mills Memorial Hospital at Golden Gateway Holiday Inn, San Francisco. Monday-Friday. 32 hrs. $200. Contact: Robert Siegel, MD, Med. Staff Office, Mills Memorial Hosp., 100 S. San Mateo Dr., 94401. (415) 342-5667.

September 9-14—**Non-Invasive Diagnostic Technique in Vascular Disease.** UCSD at Sheraton Harbor Island Hotel, San Diego. Sunday-Friday. 35 hrs. $300.

September 16-20—**Pacific Dermatologic Association—Annual Meeting.** Hyatt Regency, San Francisco. Sunday-Thursday. 15½ hrs. Contact: Florence Beardsley, Exec. Sec., PDA, 180 Mark Twain Ave., Reno NV 89509. (702) 323-2461.

September 24-28—**An Advanced Course for Internists.** STAN at San Francisco. Monday-Friday.

September 24-28—**Vascular Medicine and Surgery.** STAN at Stanford Court, San Francisco. Monday-Friday. 25 hrs. $290.

September 28-30—**Coronary Disease, Exercise Testing and Cardiac Rehabilitation.** International Medical Education Corp. at Sheraton on the Wharf, San Francisco. Friday-Sunday. 13 hrs. $202. Contact: Stephen E. Mattingly, IMEC, 64 Inverness Dr. E., Englewood, CO 80110. (800) 525-8646.

October 3-4—**47th Annual Fall Symposium and 12th George C. Griffith Scientific Lecture.** American Heart Assn., Greater Los Angeles Affiliate, at Hilton Hotel, Los Angeles. Wednesday-Thursday. 12 hrs. $85, member any Heart Assn.; $110, nonmember. Contact: Alexis Krieger, AHA, 2405 W. 8th St., Los Angeles 90057. (213) 385-4231.

October 8—**Calcium Metabolism.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

October 11-12—**49th Annual Physicians' Postgraduate Symposium on Cardiovascular Disease.** American Heart Assn., San Francisco Chapter, at San Franciscan Hotel, San Francisco. Thursday-Friday. Contact: Patty MacJennett, AHA, 421 Powell St., San Francisco 94108. (415) 433-2273, ext. 443.

October 15-19—**Advanced Course for Internists.** STAN at Hyatt on Union Square, San Francisco. Monday-Friday. 25 hrs. $290.

October 18-21—**Society of Nuclear Medicine—4th Annual Western Regional Meeting.** Monterey Conference Center, Monterey. Thursday-Sunday. Contact: Justine Parker, Western Regional Chapters, Society of Nuclear Medicine, P.O. Box 40279, San Francisco 94140. (415) 647-0722.

October 20-27—**British Clinical Cardiology in the Paul Wood Tradition.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 29 hrs. $325.

October 22—**Respiratory Diseases Due to Pollutants.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

OBSTETRICS AND GYNECOLOGY

August 6-12—**Reproductive Endocrinology, Infertility and Contraception.** USC at Royal Lahaina Hotel, Maui, Hawaii. One week. 24½ hrs. $300.

August 25-31—**Edward Tyler Symposium on the Practical Management of the Infertile Couple—3rd Annual.** Tyler Medical Clinic, Los Angeles, and Univ. of Hawaii School of Medicine at Maui Surf Hotel, Maui, Hawaii. One week. 16 hrs. $200. Contact: Jetset Tours, 2029 Century Park East, Suite 2130, Los Angeles 90067.

PEDIATRICS

June 18-20—**Pediatric Gastroenterology.** UCSF at Golden Gateway Holiday Inn, San Francisco. 13 hrs. $225.

July 28—**The Child's Hip: A Program for the Primary Care Physician.** UCD at Red Lion Motor Inn, Sacramento. Saturday. 7 hrs.

August 4—**Pediatric Dermatology Seminar.** See Medicine, August 4.

October 13-18—**American Academy of Pediatrics—Annual Meeting.** Hilton Hotel and Brooks Hall, San Francisco. One week. 33-36 hrs. $60, members; $120, nonmembers. Contact: W. G. Janzen, Meeting Mgr., AAP, 1801 Hinman Ave., Evanston, IL 60204. (312) 869-4255.

PSYCHIATRY

June 15-July 28—**Summer Gerontology Institute.** San Jose State University. 6 weekend workshops. Contact: Cont. Ed., SJSU, San Jose 95192. (408) 277-2182.

June 16-23—**Comparative Psychiatric Therapies: Dynamic, Behavioral, and Pharmacological Approaches.** USC at Royal Lahaina, Maui, Hawaii. One week. 26¾ hrs. $300.

July 21-22—**Medical Aspects of Psychiatric Practice.** UCLA. Saturday-Sunday. 9 hrs. $150.

September 10—**Ambulatory Treatment of the Depressed Patient.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

September 15—**Psychopharmacology in Clinical Practice: A Practicum in Mind-Allergy Drugs.** UCLA. Saturday.

October 27—**Psychiatry Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Saturday. 7 hrs. Contact: Prog. Coordinator, UCI Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 595-3811.

October 28-31—**Academy of Psychosomatic Medicine—Annual Meeting.** Fairmont Hotel, San Francisco. Sunday-Wednesday. Contact: Thomas C. Nelson, Exec. Dir., 70 W. Hubbard, Suite 202, Chicago, IL 60610. (312) 644-2623.

RADIOLOGY AND PATHOLOGY

June 20-22—**Symposium on Emergency Room Radiology.** See Emergency Medicine, June 20-22.

July 28-August 4—**Medical Imaging.** American College of Medical Imaging at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. Contact: ACMI, P.O. Box 27188, Los Angeles 90027. (213) 275-1393.

September 13-May 8—**L.A. Bone and Joint Clinico-Pathological-Radiological Correlation and Conference.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. 2nd Thursday of each month. 3 hrs./session. Contact: Prog. Coord., Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 80801. (213) 595-3811.

October 18-21—**Society of Nuclear Medicine—4th Annual Western Regional Meeting.** See Medicine, October 18-21.

Postgraduate Videotape Programs in Diagnostic Radiology. Developed by Dept. of Radiology, UCSF. 15 programs in all aspects of diagnostic radiology. Outstanding group of national and international guest lecturers in addition to UC staff present basic approaches to radiographic interpretation and technique as well as new research and clinical advances. Contact: Aveleen Blumenstock, Videotape Coordinator, Dept. of Radiology, UCSF, San Francisco 94143. (415) 666-1988.

SURGERY

June 16—**Abdominal Injuries.** See Emergency Medicine, June 16.

July 23-24—**Microcirculatory Approach to Current Medical and Surgical Problems.** See Medicine, July 23-24.

August 4-11—**Ophthalmology.** USC at Mauna Kea Beach Hotel, Kamuela, Hawaii. One week. 28 hrs. $325.

August 20—**Fluid-Electrolyte Problems in the Surgical Patient.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

September 24—**Trauma—Auto and Motorcycle Patients.** See Emergency Medicine, September 24.

September 24-28—**Vascular Medicine and Surgery.** See Medicine, September 24-28.

October 4-6—**Advances and Controversies in Vascular Surgery.** Cedars-Sinai Medical Center at Century Plaza Hotel, Los Angeles. Thursday-Saturday. 19 hrs. $195. Contact: Lore Kahane, Room 2049, Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles 90048. (213) 855-5547.

October 6—**Update of Pediatric Opthalmology.** Jules Stein Eye Institute, Los Angeles. Saturday. 8 hrs. $85. Contact: Lu Hendricks, Jules Stein Eye Inst., UCLA Sch. of Med., Ctr. for Health Sciences, Los Angeles 90024. (213) 825-4617.

October 11-13—**Surface Replacement.** UCLA. Thursday-Saturday.

October 19-20—**Cataract Surgery Pragmatics.** Memorial Hospital Medical Center-UCI Center for Health Education, Long Beach. Friday-Saturday. 14 hrs. $150. Contact: Program Coordinator. Ctr. for Health Education, 2801 Atlantic Ave., Long Beach 90801. (213) 585-3811.

October 28-November 9—**Temporal Bone Surgical Dissection Course.** Ear Research Institute, Los Angeles. Two weeks. $1,200, otolaryngologists; $900, residents. Contact: Antonio De La Cruz, MD, Ear Research Inst., 256 S. Lake St., Los Angeles 90057.

OF INTEREST TO ALL PHYSICIANS

June 23-30—**Manipulative Medicine.** USC at Sheraton-Waikiki, Hawaii. One week. $325.

July 9—**Practical Approach to the Drug Dependent Patient.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

July 19-21—**Tissue Fluid Pressure and Composition.** UCSD. Thursday-Saturday. 17 hrs. $190.

August 4-11—**Hypnosis and Imagery: Practical Applications.** Bay General Community Hosp., Chula Vista, at Hotel Intercontinental, Maui, Hawaii. One week. 15 hrs. $150. Contact: Errol R. Korn, MD, 480 4th Ave., Suite 409, Chula Vista 92010. (714) 420-8051.

August 6—**The Seductive Patient.** UCSF at Eden Hospital, Castro Valley. Monday. 2 hrs.

August 11-22—**Postgraduate Refresher Course—22nd Annual.**

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August 19-24—**Family Practice Refresher Course—7th Annual.** UCD at Del Monte Hyatt, Monterey. One week. 30 hrs. $225.

August 25-31—**Edward Tyler Symposium on the Practical Management of the Infertile Couple—3rd Annual.** See Obstetrics and Gynecology, August 25-31.

September 1-8—**Manipulation, Mobilization and Related Techniques in the Treatment of Musculo-Skeletal and Myofascial Pain Syndromes.** USC at Sheraton Waikiki Hotel, Hawaii. One week. 27½ hrs. $325.

September 9-13—**American Academy for Cerebral Palsy and Developmental Medicine—Annual Meeting.** St. Francis Hotel, San Francisco. Sunday-Thursday. 26 hrs. $95. Contact: Helen Bryan, Assoc. Exec. Dir., 1255 New Hampshire Ave. NW, #1030, Washington, DC 20036. (202) 659-8251.

September 13-14—**Long Term Care Programs for the Elderly.** UCLA at Biltmore Hotel, Los Angeles. Thursday-Friday.

September 14-15—**The Last Horizon: Practical Solutions to Improved Patient Care of Patients with Terminal Illness.** UCD at Hyatt Lake Tahoe. Friday-Saturday. 15 hrs.

September 15—**Psychopharmacology in Clinical Practice: A Practicum in Mind-Allergy Drugs.** See Psychiatry, September 15.

September 20—**California Venereal Disease Controllers' Clinical Session.** CMA Task Force on Venereal Disease, Calif. VD Controllers Assn. and Calif. Academy of Preventive Medicine at San Mateo. Thursday. Contact: Karin McGhee, CMA.

October 11-13—**Western Occupational Medical Association.** Monterey. Thursday-Saturday. Contact: B. H. Bravinder, P.O. Box 201, Alamo 94507.

October 13-21—**International Body Imaging Conference—4th Annual.** West Park Hospital at Royal Lahaina Hotel, Maui, Hawaii. 9 days. 30 hrs. $295. Contact: Conference Sec., Imaging Conf., West Park Hospital, Dept. of Radiology, 22141 Roscoe Blvd., Canoga Park 91304.

October 14-15—**Advances in Alcoholism Symposium.** UCSD and Raleigh Hills Foundation at Newporter Inn, Newport Beach. Sunday-Monday. 14 hrs. $150. Contact: Robert E. Schmitz, MD, Raleigh Hills Fnd., 881 Dover Dr., No. 20, Newport Beach 92663. (714) 645-4310.

October 20—**Exercise Medicine.** UCLA. Saturday.

Videotape Postgraduate Course for the Primary Care Physician. UCSF, School of Medicine, Div. of Ambulatory and Community Medicine. 24 Category I hrs. upon completion of course as designed—12 programs each year. Contact: Ms. Estelle Nelson, UCSF, Rm. 432-A, 400 Parnassus Ave., San Francisco 94143. (415) 666-1445.

OREGON

COUNCIL ON MEDICAL EDUCATION

This bulletin of information regarding continuing education programs and meetings of various medical organizations in Oregon is supplied by the Council on Medical Education of the Oregon Medical Association. In order that they may be listed here, please send communications relating to your future meetings or postgraduate courses two months in advance to Council on Medical Education, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201; or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470

Every Monday 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470.

University of Oregon Medical School, Department of Psychiatry, 3181 SW Sam Jackson Park Road, Portland 97201:

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Every Wednesday, 4:00 p.m. to 5:00 p.m.—**Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, University of Oregon Medical School. Contact: Dept. of Psychiatry, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201.

University of Oregon Medical School, Department of Medicine, 3181 SW Sam Jackson Park Road, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m.—**Department of Medicine Grand Rounds.** Library Auditorium, University of Oregon Medical School. Contact: Dept. of Medicine, University of Oregon Medical School, 3181 SW Sam Jackson Park Road, Portland 97201.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Contact: Chris Cobb, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210.

Providence Medical Center, 700 NE 47th Ave., Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Martha Regan, MD, Providence Medical Center, 700 NE 47th Ave., Portland, 97213.

Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227

Every Thursday at 12:30 p.m. **Basic Science for Clinicians.** Contact: Ben Bachulis, MD, Emanuel Hospital, 2801 N Gantenbein Street, Portland 97227.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter St. SE, Salem 97301.

FAMILY PRACTICE

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, University of Oregon Health Sciences Center, Portland. Contact: William A. Fisher, MD, University of Oregon Health Sciences Center, Department of Family Practice, 3181 SW Sam Jackson Park Road, Portland 97201.

February 11-16—**Eleventh Annual Family Practice Review.** Portland. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

OBSTETRICS AND GYNECOLOGY

October 22-24—**Third Annual Pacific Northwest Review of Obstetrics and Gynecology.** Jantzen Beach Red Lion, Portland. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

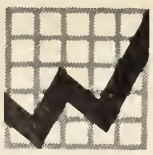
OF INTEREST TO ALL PHYSICIANS

June 23—**Progress and Controversy in Fertility Regulation.** Sheraton Lloyd Center, Portland. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Education, University of Oregon Health Sciences Center, 3181 SW San Jackson Park Road, Portland 97201.

September 14-15—**Newer Concepts in Cardiology.** Ashland Hills Motel, Ashland. Contact: J. S. Reinschmidt, MD, Director, Division of Continuing Education, University of Oregon Health Sciences Center, 3181 SW Sam Jackson Park Road, Portland 97201.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. Please send information to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle 98121; or phone (206) 623-4801.



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June 21-23—**American College of Cardiology: Medical and Surgical Management of Coronary Artery Disease.** Seattle, Thursday-Saturday. Virginia Mason Medical Center. Contact: Barbara Gould, Virginia Mason Medical Center, 1100 Ninth Ave., Seattle, WA 98101. (206) 223-6898.

June 23-24—**The American Medical Heritage: Hematic, Heroic and Heretical.** Sun Valley, Idaho, Saturday-Sunday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

June 25-26—**Platelets and Clotting—Univ. of Wash. Internal Medicine Review Sessions.**

June 25—Monday, Wenatchee. 7:30-9:30 p.m., Wenatchee Valley Clinic. Contact: William McKee, MD, Wenatchee Valley Clinic, PO Box 489, Wenatchee, WA 98801. (509) 663-8711.

June 26, Tuesday, Yakima. 5-7 p.m., Memorial Hospital. Contact: Harry Kimball, Yakima Medical Center, Suite 5, Yakima, WA 98902. (509) 575-7666.

August 16-18—**Controversies in Otolaryngology.** Seattle. Thursday-Friday. Washington Plaza Hotel. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

September 23-24—**Medical Problems in the Surgical Patient.** Walla Walla. Sunday-Tuesday. Walla Walla General Hospital. Contact: Sharon Werner, Walla Walla General Hospital, 933 Bonsella, Walla Walla, WA 99362. (509) 522-0480, Ext. 543.

October 5-6—**Scientific Program, Annual Meeting, Washington State Medical Association.** Seattle. Friday-Saturday. Washington Plaza Hotel. Contact: Mr. George Morford, Washington State Medical Association, 2033 Sixth Avenue, Seattle, WA. (206) 623-4801.

ALASKA, MONTANA AND IDAHO

This list of continuing education programs in Alaska, Montana and Idaho is supplied by the University of Washington School of Medicine's program of regional medical education in Washington, Alaska, Montana and Idaho (WAMI). To have events listed, please send information to: WAMI Program, CME Calendar, D-207 Health Sciences Building, School of Medicine, SC-64, University of Washington, Seattle, Washington 98195; or phone (206) 543-6995.

ALASKA

June 27—**Diabetes in Pregnancy—Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hos-

WESTERN STATES MEDICAL ASSOCIATION MEETINGS

Alaska State Medical Association—1135 W. 8th Ave., Anchorage 99501. Annual Meeting: June 6-8, 1979, Shee Atika Lodge, Sitka.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. Annual Meeting: April 23-27, 1980, Registry Resort, Scottsdale.

California Medical Association—731 Market St., San Francisco 94103. Annual Meeting: February 7-13, 1980, Town and Country, San Diego.

Colorado Medical Society—1601 E. 19th Ave., Denver 80218. Annual Meeting: September 19-23, 1979, the Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. Annual Meeting: October 8-12, 1979, Ilikai Hotel, Honolulu.

Idaho Medical Association—407 W. Bannock St., P.O. Box 2668, Boise 83701. Annual Meeting: June 20-23, 1979, Sun Valley.

Montana Medical Association—2021 11th Ave., Suite 12, Helena 59601. Annual Meeting: October 4-6, 1979, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. Annual Meeting: 1980—date and place to be announced.

New Mexico Medical Society—2650 Yale SE, Albuquerque 87106. Annual Meeting: 1980—date and place to be announced.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. Annual Scientific Meeting: November 2-4, 1979, OMA Headquarters.

Utah State Medical Association—42 S. 5th East St., Salt Lake City 84102. Annual Meeting: September 11-14, 1979, Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. Annual Meeting: October 4-7, 1979, Washington Plaza Hotel, Seattle.

Wyoming State Medical Society—P.O. Drawer 4009, Cheyenne 82001. Annual Meeting: August 28-31, 1979, Jackson Lake Lodge, Moran.

pital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

July 25—**Herpes Genitalis—Univ. of Wash. OB-GYN Sessions** (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

August 22—**Dysplasia and Early Cervical Neoplasia**—Univ. of Wash. OB-GYN Sessions (Anchorage). Wednesday. 12 noon, Providence Hospital. Contact: Hedric B. Hanson, MD, 3300 Providence Dr., Suite 212, Anchorage, AK 99504. (907) 276-8385.

MONTANA

June 21-23—**Montana Academy of Family Physicians' 29th Annual Scientific Assembly.** Fairmont Hot Springs. Thursday-Saturday. Contact: R. Bruce Beithon, MD, Twin Bridges, MT 59754. (406) 684-5642.

June 29-30—**Respiratory Therapy and Blood Utilization.**

June 29, Friday, Kalispell. 8:30 a.m.-4:30 p.m., Outlaw Inn.

June 30, Saturday, Bozeman. 8:30 a.m.-4:30 p.m. Montana State University.

Contact: Julie Wood, Montana Medical Association, 2021 Eleventh Ave., Suite 12, Helena, MT 59601. (406) 443-4000.

August 9-11—**Montana/Wyoming Chapter, American College of Surgeons' Annual Meeting**—Big Sky. Thursday-Saturday. Meadow Village. Contact: Charles F. Rinker, MD, 300 N. Willson, Bozeman, MT 59715. (406) 587-0704.

September 7-8—**Montana/Wyoming Chapter, American College of Physicians' Regional Meeting**—Fairmont Hot Springs, Friday-Saturday. Contact: J. E. McGreevey, MD, 401 S. Alabama, Butte, MT 59701. (406) 723-4384.

IDAHO

June 23-24—**The American Medical Heritage: Hematic, Heroic and Heretical**—Sun Valley. Saturday-Sunday. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

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